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PRINCIPAL INVESTIGATOR: Patricia Zilliox, Ph.D.

CONTRACTING ORGANIZATION: National Neurovision Research Institute
Owings Mills, MD 21117

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Patricia Zilliox, Ph.D.

Email: pzilliox@fightblindness.org

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14. ABSTRACT
The Foundation Fighting Blindness Clinical Research Institute (FFBCRI) [formerly National Neurovision Research Institute (NNRI)], the clinical arm of the Foundation Fighting Blindness (FFB), proposes to establish the National Eye Evaluation Research (NEER) Network to be composed of a collaborative group of five Clinical Treatment and Evaluation Centers (CTECs). The intent of this new Network is to advance the science of therapeutic and preventive interventions for inherited orphan retinal degenerative diseases and dry age-related macular degeneration (AMD) through the conduct of clinical trials and other clinically relevant research. The scope of research to be carried out encompasses: (i) Phase I and Phase II clinical trials to evaluate the safety and efficacy of new therapeutic and preventive approaches, including devices, biopharmaceuticals, small molecules, nutritional supplements, and gene transfer approaches; natural history studies to develop standardized criteria to define disease stage, severity and progression; (iii) observational studies to enhance understanding of the natural history of these diseases for different

15. SUBJECT TERMS

14. Abstract (cont.)

genotypes and phenotypes; and (iv) evaluations of the reliability and validity of different available treatment outcomes measures to determine those that are most appropriate for various genotypes and phenotypes as well as for specific interventions. The NEER Network will also develop standard protocols for data collection, maintain and expand patient databases, classified by genotype and phenotype, to allow for the timely identification of eligible patients and facilitate patient access for clinical trial participation, and design and conduct, in collaboration with the Department of Defense, training programs for military ophthalmologists in the latest technologies and diagnostic and treatment regimens.

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Introduction:

The Foundation Fighting Blindness Clinical Research Institute (FFBCRI), the clinical arm of the Foundation Fighting Blindness (FFB), has established the National Eye Evaluation Research (NEER) Network composed of a collaborative group of five Clinical Treatment and Evaluation Centers (CTECs) and a two support groups- the Clinical Coordinating Center and an independent visual image reading center. The intent of this Network remains the same as in the original application: to advance the science of therapeutic and preventive interventions for inherited orphan retinal degenerative diseases and dry age-related macular degeneration (AMD) through the conduct of clinical trials and other clinically relevant research. The scope of research to be carried out encompasses:

- Phase I and Phase II clinical trials to evaluate the safety and efficacy of new therapeutic and preventive approaches, including devices, biopharmaceuticals, small molecules, nutritional supplements, and gene transfer approaches;
- natural history studies to develop standardized criteria to define disease stage, severity and progression;
- observational studies to enhance understanding of the natural history of these diseases for different genotypes and phenotypes; and
- evaluations of the reliability and validity of different available treatment outcomes measures to determine those that are most appropriate for various genotypes and phenotypes as well as for specific interventions.

The NEER Network has and will continue to revise standard protocols for data collection, maintain and expand standardized patient databases, classified by patient genotype and phenotype, to allow for the timely identification of eligible patients and facilitate patient access for clinical trial participation. In addition, the NEER network will design and conduct, in collaboration with the Department of Defense, training programs for military ophthalmologists in the latest technologies and diagnostic and treatment regimens. An important part of the raison d'être for NEER is that military population mirrors the civilian population, including the incidence of retinal diseases. Soldiers and their families therefore suffer from the same sight-robbing retinal degenerative diseases as the general population. In addition, the military has an expanding retiree population that will suffer from age-related macular degeneration (AMD) and any useful preventative or treatment regimen will greatly enhance these persons lives by preventing them from losing vision.

The NEER network, in cooperation with COL Donald A. Gagliano, MD, MHA, DOD, Principal Advisor for Vision, Director, DODNA Vision Center of Excellence, and others in DOD as appropriate will actively develop a program to include military hospitals and ophthalmologists in clinical trials for Retinal Degenerative Diseases so that military personnel and their families will directly benefit from the new preventions, treatments and cures for these sight robbing diseases. In addition, the NEER network will work with the appropriate military office to develop a fellowship and senior physician training and continuing education program for military ophthalmologists to obtain specialized training at NEER network academic centers in the latest technologies, including non-invasive imaging such as multifocal electroretinogram (mfERG), optical coherence tomography (OCT), and Adaptive Optic Scanning Laser Ophthalmoscopes (AOSLO).

Body:
The Foundation Fighting Blindness Clinical Research Institute (FFBCRI), the clinical arm of the Foundation Fighting Blindness (FFB), has established the National Eye Evaluation Research (NEER) Network composed of a collaborative core group of five (5) Clinical Treatment and Evaluation Centers (CTECs). The intent of the NEER Network is to advance the science of therapeutic and preventive interventions for inherited orphan retinal degenerative diseases and dry age-related macular degeneration (AMD). This will be accomplished within the NEER Network through the conduct of clinical trials and other clinically relevant studies. Pertinent background information on the FFB, the FFBCRI, the retinal diseases to be studies, and the rationale underlying the need for and feasibility of this new Network are delineated below.

The FFB is the world's largest source of non-governmental support for research on inherited orphan retinal degenerative diseases and dry AMD. Since its inception in 1971, the Foundation has raised more than $450 million and, in the current fiscal year, is providing over $17.7 million in funding for 130 grants, including the modules of 15 Centers. The research projects of these grants are conducted by 190 research investigators at 73 Institutions, Eye Hospitals and Universities. In addition to funding researchers within the United States, FFB funding extends internationally including laboratories in Canada, England, France, Germany, Italy, Israel, China, and the Netherlands.

To promote collaborations between basic and clinical researchers and accelerate the advancement of promising preventive and therapeutic approaches to the clinic, the Foundation also supports Research Centers internationally. This Research Center Program involves inter-disciplinary groups of investigators conducting multiple research projects with an emphasis on translational research to facilitate clinical applications and the sharing of research tools, knowledge and data.

In 2003, the Foundation established the FFBCRI (formerly known as the National Neurovision Research Institute or NNRI), a non-profit entity, to capitalize on the fairly recent emergence of therapeutic and preventive products and devices that require rigorous clinical evaluation for safety and efficacy. The mission of the FFBCRI is to accelerate the translation of promising research on treatment and prevention approaches into clinical trials. On July 1, 2012, the FFBCRI was renamed the Foundation Fighting Blindness Clinical Research Institute in order to provide a better message that reinforces the link between FFBCRI and the Foundation Fighting Blindness.

Inherited orphan retinal degenerative diseases are a family of inherited pathologies with the ultimate consequence of photoreceptor death and severe visual impairment usually ending in blindness. In the United States, the total number of individuals affected by retinitis pigmentosa (RP) and other forms of rare inherited retinal degenerative diseases is estimated at approximately 200,000 individuals. RP, Stargardt disease[1], and Usher syndrome represent the predominant forms of inherited orphan retinal degenerative diseases and are estimated to affect ~80,000 ~100,000, ~25,000, and ~20,000 individuals in the U.S., respectively. Genetic heterogeneity is a key feature of each of these predominant diseases. To date, over 200 genes with mutations causing one or more forms of inherited orphan retinal degenerative diseases have been cloned, and over 50 more have been identified based on candidate gene studies or linkage mapping.

In the majority of inherited orphan retinal degenerative diseases, visual impairment is detected in the first or second decade of life. Assuming that 30% of individuals will reach legal blindness by their third decade of life, 30% by the fourth decade of life, 30% by the fifth decade of life, while 10% never reach legal blindness, and considering just the annual cost of blindness to the U.S. government, adjusted annually for inflation at a rate of 2.5%, then the cumulative minimal lifetime costs incurred by the U.S. government for the current civilian and military populations affected by inherited orphan retinal degenerative diseases is more than $38 billion. This tremendous economic burden will not only continue to be incurred, but will increase unless efforts are made to define the molecular, biochemical and clinical parameters of these diseases and to advance capabilities to a point where rational, safe therapeutic strategies can be designed, tested and adopted as standard care.

While repeat evaluation and study of affected patients are vital to rigorously characterize the unique features of various diseases and the factors that cause disease progression, several obstacles, in addition to the lack of research funding, often prevent the necessary frequency and thoroughness of patient examination. First, patients are often diagnosed by ophthalmologists who have limited training in the diagnosis and management of patients with rare forms of inherited orphan retinal degenerative diseases. Second, once patients are informed of the current lack of treatment options for their disease condition, they have little incentive for engaging in repeat clinical evaluations. Third, and perhaps more rare than the diseases themselves, is the number of clinicians fully trained in both the clinical and genetic aspects of inherited orphan retinal degenerative diseases. Training of additional clinical specialists in diagnostic and genetic evaluation of patients with rare forms of inherited retinal degenerative diseases has been identified as one of the most important resources needed to ensure that therapies for these diseases reach the clinic.

While inherited orphan retinal degenerative diseases account for a small portion of all vision loss, dry age-related macular degeneration accounts for approximately 90 percent of all age-related macular degeneration (AMD), affecting over 7 million individuals in the United States alone. With dry AMD yellow-white deposits composed of waste products from photoreceptor cells, called drusen, accumulate in the retinal pigment epithelium (RPE) tissue beneath the macula. The RPE tissue can lose its ability to process waste and drusen deposits accumulate in the RPE, reasons for this are being investigated with FFB support. These deposits are thought to interfere with the function of photoreceptors and the RPE in the macula, causing progressive degeneration of these cells with the eventual loss of vision.

Vision loss from dry AMD occurs very gradually over the course of many years. Central vision may even remain stable between annual eye examinations, and individuals with dry AMD do not usually experience a total loss of central vision. However, vision loss may make it difficult to perform tasks that require finely focused vision (e.g., driving or reading). Although there are extensive research efforts underway to identify treatments for dry AMD, at this time the only proven treatment for late-stage drug AMD is the Age-Related Eye Disease Study (AREDS) antioxidant supplement regimen, stopping smoking, and eating healthfully.

Through the research programs conducted with the support of the FFB and, more recently, through the FFBCRI, and the National Eye Institute of the National Institutes of Health (NIH), basic scientific discoveries have shown that selected nutritional factors, neuroprotective drugs, and gene therapies are safe and can prevent visual loss or restore visual function in preclinical animal models of certain genetically defined forms of inherited orphan retinal degenerative disease and dry AMD. While AREDS antioxidant formulation is a widely accepted treatment, clinical trials of other potentially more effective treatments are imminent.

Recent progress in the classification of mutations for various inherited orphan retinal degeneration and dry AMD genotypes and the development of treatment possibilities raise the likelihood that potential treatments will be ready for evaluation in clinical trials in the near future. Unfortunately, there are considerable obstacles to the successful conduct of these clinical trials, including:

- lack of resources for the design and conduct of effective and efficient clinical trials for inherited orphan retinal degenerative diseases and dry AMD;
- limited number and wide geographic distribution of potentially eligible patients across the U.S., making follow up examinations at one clinical center financially and logistically problematic, if not unfeasible;
- limited number of retinal specialists with expertise in these diseases;
- use of diverse, non-uniform approaches to measuring disease severity, stage and progression; and
- unresolved methodologic issues, such as determination of clinically meaningful, reliable and valid outcome measures.

The development of a clinical trials network has already shown its efficacy in being an efficient and valuable approach to overcome these obstacles and to maximize the resources

currently available (see below report on the ongoing VPA clinical trial in the NEER network for autosomal dominant retinitis pigmentosa). As new interventions become available for clinical evaluation, the creation of such a network will provide the infrastructure necessary to facilitate the initiation and conduct of properly designed clinical trials of investigational therapeutic and preventive approaches and devices in a timely manner. The development of a clinical trials network in inherited orphan retinal degenerations and dry AMD will require the cooperation of an interdisciplinary team with clinical, genetic, and basic science expertise.

Key Research Accomplishments:

NOTE: In 2010, the FFBCRI worked with TATRC to apportion the two grants it has received (-0189 and -0720) into consistent expenses. It was submitted and approved by TATRC that the -0189 grant would support the NEER infrastructure (this report) while the -0720 grant would support the actual clinical trial and natural history studies, including CTEC costs associated with these functions. The annual reports for both these grants will be the same from the Key Research Accomplishments and Reportable Outcomes perspective as these two grants support the overall operation of the NEER network.

The third Steering Committee meeting of the NEER Network took place in June 2011 (see appendices for minutes[1]), at which time the committee reviewed the UCSD CTEC/Dr. William Freeman's results for his natural history studies for dry age-related macular degeneration, with an eye toward using this data to inform a natural history study for inherited orphan retinal degenerations. Dr. Freeman has been piloting this and collecting data so a standardized protocol and data collection can be developed and implemented at all CTECs. A final report from UCSD was obtained (see appendices for UCSD final report[2]).

In 2011-2012, the NEER network continued its first clinical trial using the University of Utah CTEC as the nucleating Center for the trial and 5 recruitment sites to ensure adequate enrollment- the Retina Foundation of the Southwest, Dallas, TX; the University of Miami, Miami, FL; the University of Tennessee, Memphis, TN; the Oregon health & Sciences University, Portland, OR; and the University of Michigan, Ann Arbor, MI. The EMMES Corporation is the NEER Clinical Coordinating Center and the Translational Clinical Trials Center (TCTC) at the Casey Eye Institute, Oregon Health and Science University (OHSU) as the independent image Reading Center for all NEER clinical trials. NEER's first clinical trial is progressing on an expanded schedule to ensure adequate recruitment of subjects. Eighty-four subjects have been screened, 32 subjects have been randomized, and 11 potential subjects are currently undergoing screening procedures. The Central Reading Center has trained and certified all clinical site ophthalmic personnel on required study procedures. Existing web-based data collection systems that were implemented by the NEER Coordinating Center for the current clinical trial have been operating as anticipated and monitoring visits are ongoing. NEER personnel at FFBCRI attended specialized training for up-to-date skills in Clinical Document Management.

The Data Safety Monitoring Board (DSMB) Safety Committee met twice this year. The Committee reviewed VPA study progress and did not note any safety issues of concern (see appendices for DSMB summaries[3,4]).

The next large NEER study currently being planned is a natural history study of Stargardt's disease utilizing the staff of the Wilmer Eye Institute CTEC at the Johns Hopkins University as the lead Principal Investigator. A feasibility study was completed in May 2012 (see appendices for ProgStar Feasibility Study[5]). A subsequent project design meeting, with representatives from eight premier inherited retinal disease research sites from 4 countries and the National Eye Institute, was held in August 2012 (see appendices for ProgStar Design Meeting Minutes[6]) and the study protocol is currently under development. Data collection is estimated to start in the first quarter of 2013.

Reportable Outcomes:

The FFBCRI NEER Network:

- Continuing recruitment of participants into NEER clinical trial for autosomal dominant retinitis pigmentosa at six sites- the CTEC site at University of Utah and five recruitment sites- the Retina Foundation of the Southwest, Dallas, TX; the University of Miami, Miami, FL; the University of Tennessee, Memphis, TN; the Oregon health & Sciences University, Portland, OR; and the University of Michigan, Ann Arbor, MI. The protocol is to test a FDA approved drug (valproic acid) in individuals with autosomal dominant retinitis pigmentosa.
    - Eighty-four subjects have been screened, 32 subjects have been randomized, and 6 potential subjects are currently undergoing the screening procedures.
    - The Central Reading Center has trained and certified all clinical site ophthalmic personnel on required study procedures.

- Existing web-based data collection systems that were implemented by the NEER Coordinating Center for the current clinical trial have been operating as anticipated and monitoring visits are ongoing.

- Working with the Wilmer Eye Institute CTEC at the Johns Hopkins University (as the lead Principal Investigator) and eight premier inherited retinal disease research sites from 4 countries to develop the protocol for a natural history study of Stargardt's disease.
- Developed a standard protocol template for data collection that can be used in multiple studies of inherited orphan retinal degenerative diseases and dry AMD;
- Established patient databases at the University of Utah and University of Medicine and Dentistry of New Jersey CTECs, classified by genotype and phenotype, to allow for the timely identification of eligible patients and to facilitate patient access for participation in clinical trials for specific genotypes and phenotypes.

EMMES is providing the following administrative and statistical support services for the Foundation Fighting Blindness Clinical Research Institute (FFBCRI) National Eye Evaluation Research (NEER) Network:

- Participate in NEER Network Steering Committee meetings and provide statistical and design input on Concept Proposals for clinical trials/studies.
- Develop procedures and a web-based system for submission and review of Concept Proposals,
- Assist FFBCRI and the NEER Network Steering Committee in the development of a complete set of network policies,
- Conduct qualification visits for the Clinical Treatment and Evaluation Centers (CTECs) which may include GCP and GLP compliance assessments and training and certification in ETDRS Visual Acuity and Refraction,
- Provide clinical study infrastructure tools such as document templates, core data elements, reporting requirements, and study procedures.

FFBCRI has also contracted with Western Institutional Review Board (Western IRB; WIRB) to be the FFBCRI-NEER IRB of record for all clinical trials and studies.

Conclusion:

All CTECs are on board for NEER participation and have completed their initial NEER/FFBCRI contracts. In addition, the FFBCRI has implemented infrastructure support for the network (EMMES as the NEER Network Clinical Coordinating Center [NNCCC], the Translational Clinical Trials Center (TCTC) at the Casey Eye Institute, Oregon Health and Science University (OHSU) as the independent image Reading Center, and WIRB as the IRB of record for the NEER Network. FFBCRI has also continued to convene working groups of clinicians to define clinical trial parameters for inclusion/exclusion and endpoints for clinical trials in inherited retinal degenerations which are expected to be implemented in the NEER Network. The Steering Committee meeting took place on June 2011 at FFBCRI HQ to gain agreement on the primary endpoint and secondary endpoints to be used in clinical trials or interventions for Stargardt's disease (Juvenile macular degeneration) and review progress of the CTEC sites to develop NEER infrastructure. The FFBCRI and NEER, in conjunction with the National Eye Institute (NEI, NIH), hosted a meeting with the FDA to review the proposed endpoints. This meeting is an example for future meetings the FFBCRI will host with the FDA to educate them on the current clinical consensus on endpoints that make sense for clinical trials in inherited orphan retinal degenerations. The continuation of the first NEER network clinical trial and the development of the next protocol that will be implemented in the NEER network is underway. The FFBCRI is also working with both academic investigators and biotech companies on very promising leads for potential additional opportunities for the NEER network. It is anticipated that during the upcoming year, the NEER network will have two active trials enrolling participants (one clinical trial and one natural history study) ongoing.

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REVIEW

Natural History of Phenotypic Changes in Stargardt Macular Dystrophy

Saloni Walia and Gerald A. Fishman

Institute Affiliation: Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, Chicago, USA

Stargardt macular dystrophy is the most common form of juvenile onset macular degeneration. This article reviews the four stages through which this dystrophy may progress. Also, reviewed here are the variations that may be observed in the visual acuity of patients with Stargardt disease.

Keywords Stages of Stargardt macular dystrophy; visual acuity in Stargardt disease

INTRODUCTION

Stargardt macular dystrophy is the most common autosomal recessive juvenile onset macular dystrophy. The estimated prevalence of the disease is 1:8000–1:10000.[1] It was first described by Karl Stargardt in 1909.[2] Franceschetti first introduced the term fundus flavimaculatus in 1963, which referred to the presence of ill-defined yellow-white flecks in the deep retinal layers of the posterior pole.[3] Later, a number of authors concluded that both Stargardt disease and fundus flavimaculatus were the same condition.[4–7] This was later confirmed when both Stargardt disease and fundus flavimaculatus phenotypes showed disease causing mutations in the *ABCA4* gene.[8,9]

Stargardt disease is characterized by a decrease in central vision and the presence of bilateral atrophic-appearing foveal lesions. These lesions may have a beaten-metal appearance and are associated with yellow-white fundus flecks at the posterior pole and/or the midperipheral retina.[10] The age of onset is typically between 10–20 years;[10] however, a later age of onset (>20 years) is associated with a better visual prognosis.[11–13] Although a majority of patients (86%) with Stargardt disease show the presence of a dark choroid, the absence of this feature does not rule out the presence of the disease.[14]

This article demonstrates the natural history for both visual acuity loss and changes of the macula in patients with Stargardt disease who present with either foveal sparing or relative foveolar sparing. The authors also review various levels of severity in fundus findings that may be seen during the evolution of the disease.

STAGES

Based on ophthalmoscopic findings and electrophysiological and psychophysical tests, Fishman classified Stargardt macular dystrophy into four stages:[15] *Stage1:* characterized by the presence of variable pigmentary changes in the macula from initial faint and irregular pigment mottling to a beaten-metal or snail-slime appearance to an eventual atrophy of the retinal pigment epithelium (RPE) and choriocapillaries. A ring of flecks often circumscribes an area within 1 disc diameter on all sides of the fovea. Initially, relative and eventually absolute central or paracentral scotomas are seen. Normal results are most frequently obtained on electroretinogram (ERG) and electro-oculogram (EOG) testing. Lois et al. have described a reduced cone ERG in some patients at this stage.[11] *Stage 2:* characterized by the presence of fundus flecks beyond 1 disc diameter of the margin from the fovea. The flecks extend beyond the vascular arcades and often nasal to the optic disc. Partial resorption of the flecks may be observed in this stage. Peripheral visual fields are normal, a relative central scotoma may be observed in patients with macular involvement. ERG amplitudes and EOG ratios are most often normal, but subnormal cone and rod responses may be observed. Some patients may take a longer time to reach normal scotopic ERG amplitudes. These patients not infrequently manifest a prolonged period for dark adaptation (DA).

Stage 3: characterized by the presence of diffusely resorbed flecks and choriocapillaris atrophy within the macula. EOG testing shows subnormal ratios for light peak to dark trough, subnormal cone or cone and rod ERG amplitudes are

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Address correspondence to Gerald A. Fishman, MD, Department of Ophthalmology and Visual Sciences (MC 648), Room 3.85, Eye and Ear Infirmary, 1855 West Taylor Street, Chicago, Illinois 60612-7234, USA. E-mail: gerafish@uic.edu

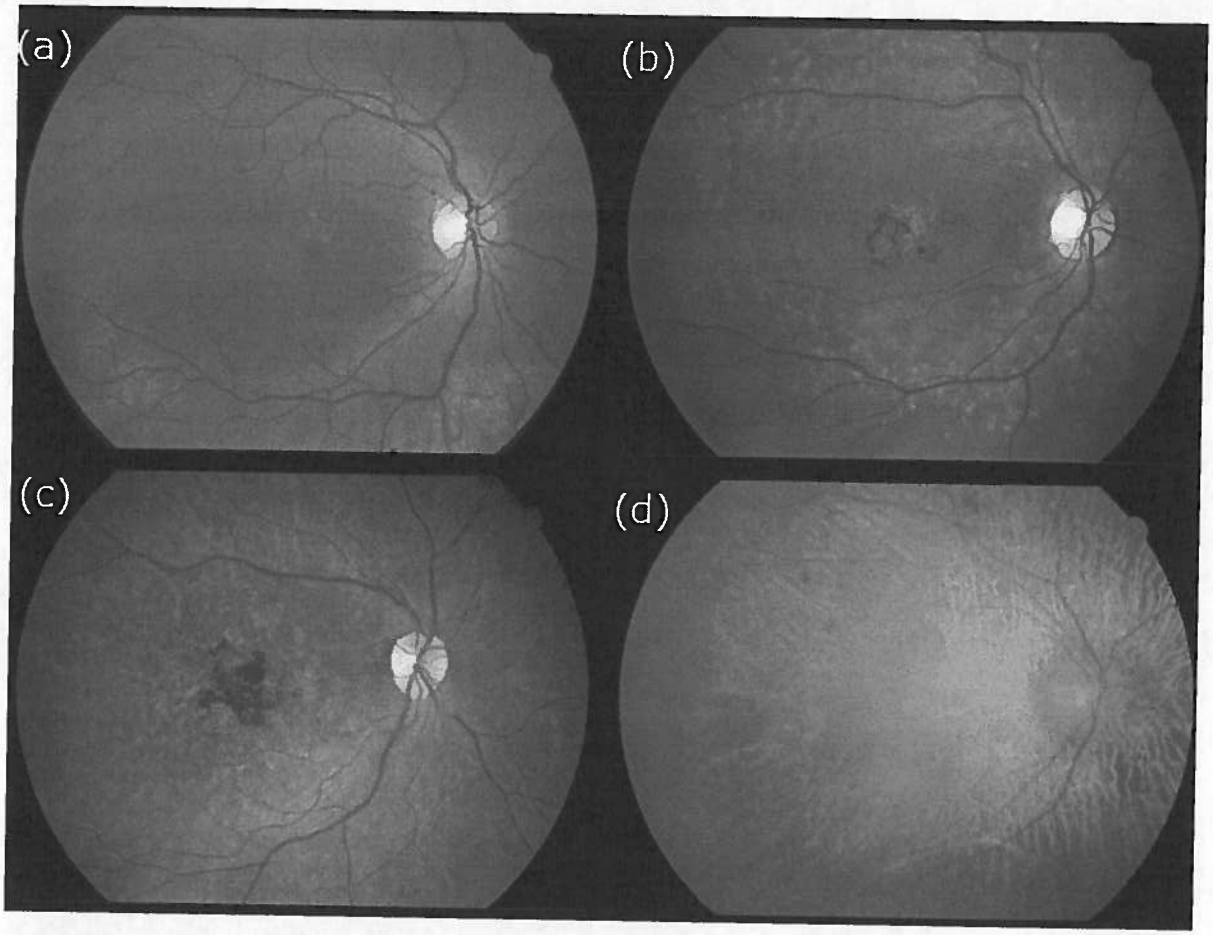

FIG. 1. Depicting Stages 1–4 in patients with Stargardt macular dystrophy. This figure has been previously published in *Ophthalmology*, 2003;110, Rotenstreich Y. et al., Visual acuity loss and clinical observations in a large series of patients with Stargardt disease, 1151–8, Copyright Elsevier.).

often recorded. DA shows a prolonged cone-rod break time and a prolonged period to reach normal or elevated rod final thresholds. Central field defects are similar to those in stage 2, however, a degree of peripheral or mid-peripheral field impairment may be evident. *Stage 4:* characterized by the presence of diffusely resorbed flecks and extensive choriocapillaris as well as retinal pigment epithelial cell atrophy throughout the fundus. Peripheral fields are moderately to extensively restricted. ERG testing shows notably reduced cone and rod amplitudes. Elevated cone and rod thresholds are seen on DA testing. These various stages of disease severity are shown in Figure 1.

It has been observed by Kim et al. that 66.1% of patients who first presented with stage 1 did not progress further to stage 2 or 3 over a median follow-up of 5.4 years. These authors noted that 69.9% of patients with an initial presentation of stage 2 remained at this stage over a median follow-up of 7.2 years and 85.7% patients with an initial stage 3 presentation did not progress to stage 4 over a median follow-up of 5.3 years (Figure 2).[16]

NATURAL HISTORY

Visual acuity in patients with Stargardt macular dystrophy usually declines to the level of 20/200 or worse. Some studies have shown that the visual acuity stabilizes after reaching 20/200 or 20/400.[12,14,16] In a study by Fishman et al., it was seen that the probability of maintaining visual acuity of 20/40 or better in at least one eye was 52% by the age of 19, 32% by age 29 and 22% by the age of 39 years.[14] Another study showed that the median time for visual acuity to decline from 20/ 40 to 20/200 was 7 years if the patient was first seen within the first two decades of life, 22 years for those first seen at ages 21–40 years, and 29 years for those who were first seen at 41–60 years of age.[12] Patients with stage 1 disease at the initial visit were more likely

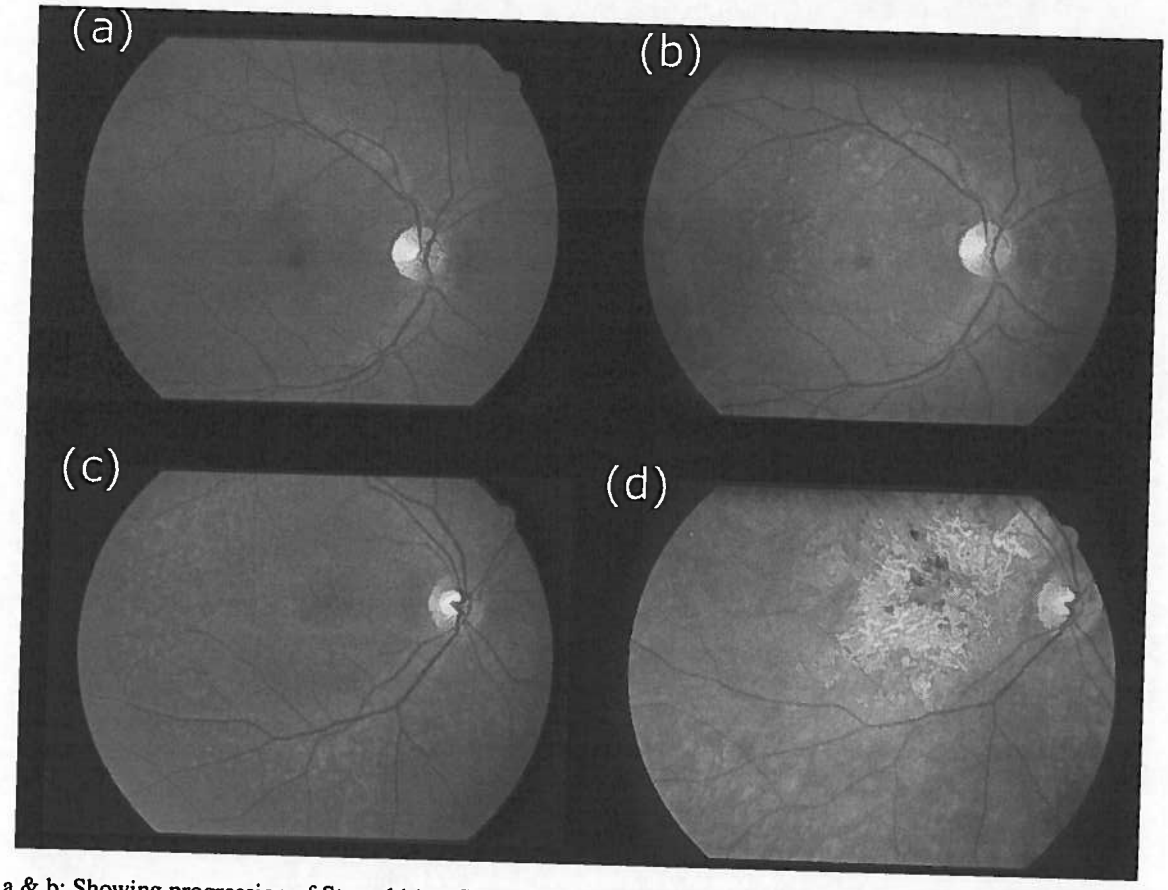

FIG. 2. a & b: Showing progression of Stage 1(a) to Stage 2(b) in a patient with Stargardt disease; c& d: Showing progression of Stage 2(c) to Stage 3(d) in another patient with Stargardt disease.

to maintain vision of 20/ 200 or better compared to patients with stage 2 or stage 2–3 disease at their initial visit.[16,17]

Previous studies have shown that patients without a clinically-observed atrophic lesion in the fovea can often maintain visual acuity of 20/40 or better.[6,12,18] One of the authors (GAF) has followed patients with Stargardt disease showing fundus foveal sparing up to 3 decades (Figure 3) and the data of visual acuity for five such patients are presented in Table 1.

Also observed was that in patients with Stargardt macular dystrophy who have an atrophic-appearing lesion in the macula but maintained a relative sparing of the central fovea (foveolar region) show a decrease in visual acuity from 20/50 to 20/200 or worse in a mean duration of 5–5.75 years. A clinically apparent worsening of the central foveal lesion is clinically evident by 3–4 years in such patients (Figure 4).

Additionally, as in patients with relative sparing of the central fovea, patients seen with the presence of macular atrophy without relative foveal sparing also can show a centrifugal expansion of their macular lesion that is clinically evident by 3–4 years from their prior visit (Figure 5).

CONCLUSION

In this article, the authors have discussed the various stages of severity that may be seen during the progression of Stargardt macular dystrophy, based upon fundus and electrophysiological findings. Various authors concur that patients with Stargardt disease who have fundus flecks and atrophic-appearing retinal changes that are limited to the macula have an overall better visual prognosis than patients with more extensive disease.[16,17,19]

Abnormalities on electrophysiological testing have also been noted in previous studies.[20–22] Lois et al. classified Stargardt macular dystrophy into three groups based on ERG findings; group 1: had severe pattern ERG abnormalities with normal scotopic and photopic ERG; group 2: showed additional loss of photopic full-field ERG function; group 3: which had a loss of both scotopic and photopic full-field ERG function.[11]

Functional abnormalities seen in Stargardt disease are due to a slowing of the retinoid cycle kinetics. Cedeciyan et al. have shown that that the initial pathophysiological process in Stargardt disease is an abnormal deposition of lipofuscin in the retinal pigment epithelium (RPE), followed by RPE degeneration

TABLE 1
Retention of good visual acuity in Stargardt disease patients with foveal sparing

Patient no.	Ages at initial and final visits	Total no. of visits	Initial VA-OD	VA at final visit-OD	Initial VA-OS	VA at final visit-OS
1	19–29 years	6	20/20	$20/25^{-1}$	20/20	$20/25^{-1}$
2	27–57 years	7	2020	$20/20^{-2}$	20/20	$20/20^{-2}$
3	26–32 years	6	$20/15^{-1}$	$20/15^{-2}$	$20/15^{-1}$	$20/15^{-1}$
4	44–66 years	4	$20/25^{-2}$	$20/25^{-2}$	$20/25^{-1}$	$20/40^{-2}$
5	49–73 years	9	$20/25^{-1}$	$20/30^{+2}$	$20/25^{-2}$	$20/25^{-2}$

*VA-Visual acuity. (RUN IN)Visual acuity has been recorded with a Snellen visual acuity chart.

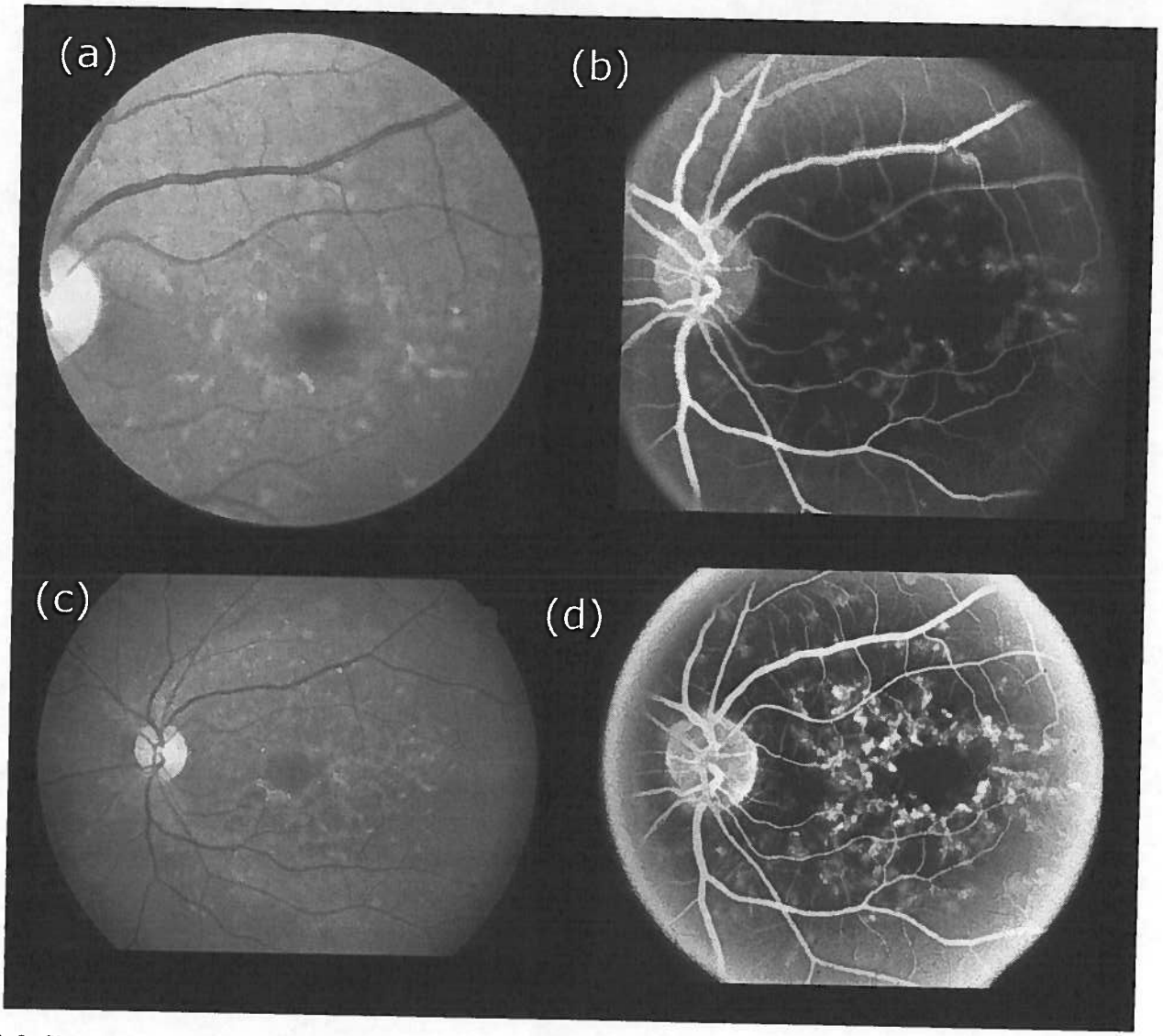

FIG. 3. Showing fundus photographs and fluorescein angiograms in the left eye of a patient with Stargardt disease and foveal sparing over 19 years. a,b: fundus photograph (a) and fluorescein angiogram (b) at the age of 49 years. Visual acuity was $20/25^{-1}$. c,d: fundus photograph (c) and fluorescein angiogram (d) of the same patient at 68 years of age. Visual acuity was $20/20^{-3}$.

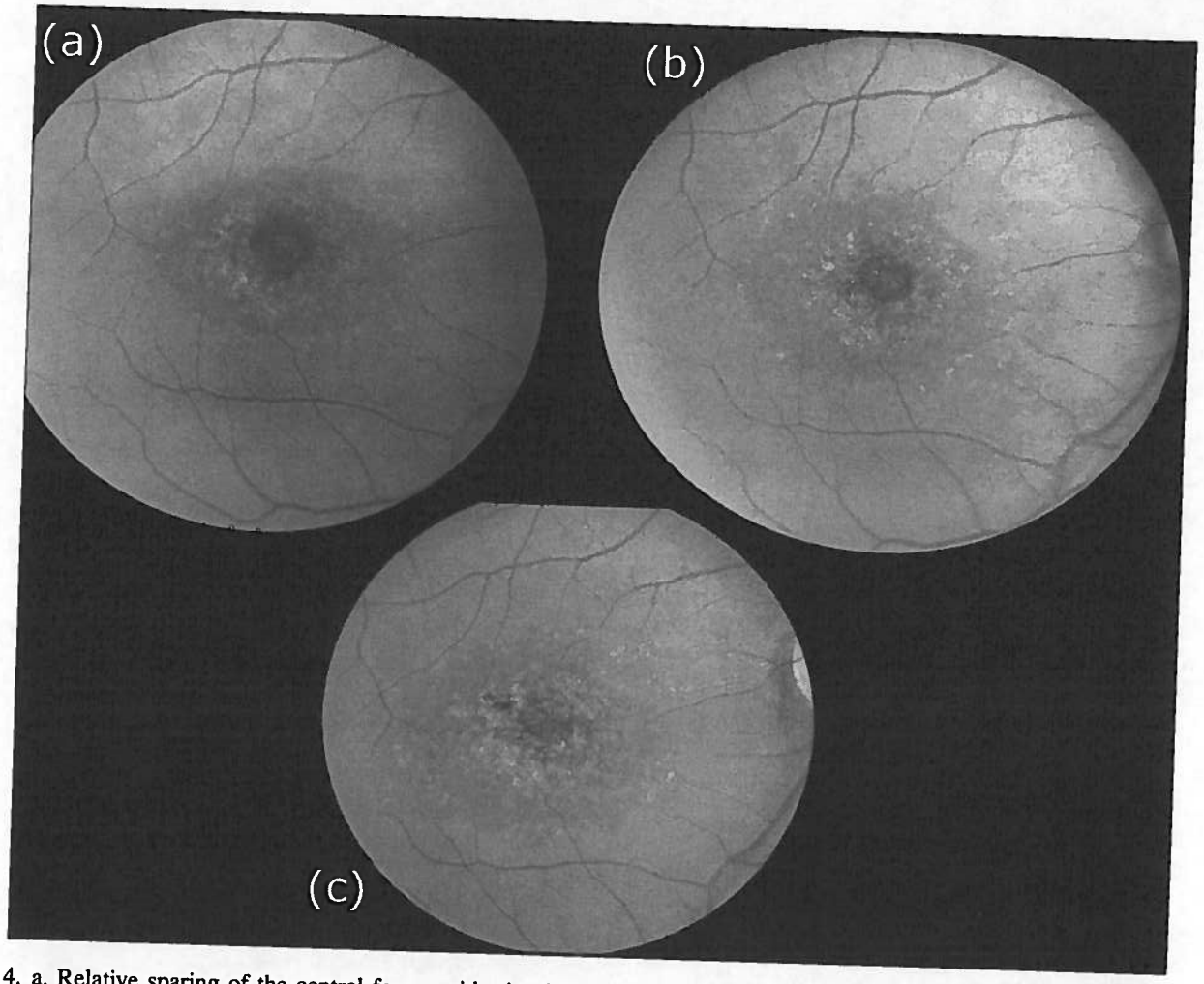

FIG. 4. a. Relative sparing of the central fovea, with visual acuity of $20/40^{-2}$. b: follow-up of the same patient after 3 years, showing an increase in the size of the macular atrophic lesion with extension toward the central fovea, visual acuity of $20/70^{+2}$. c: 6 years after the initial description, atrophic lesion extending further into the center of the fovea and expanding circumferentially more centrifugally, visual acuity of 20/200.

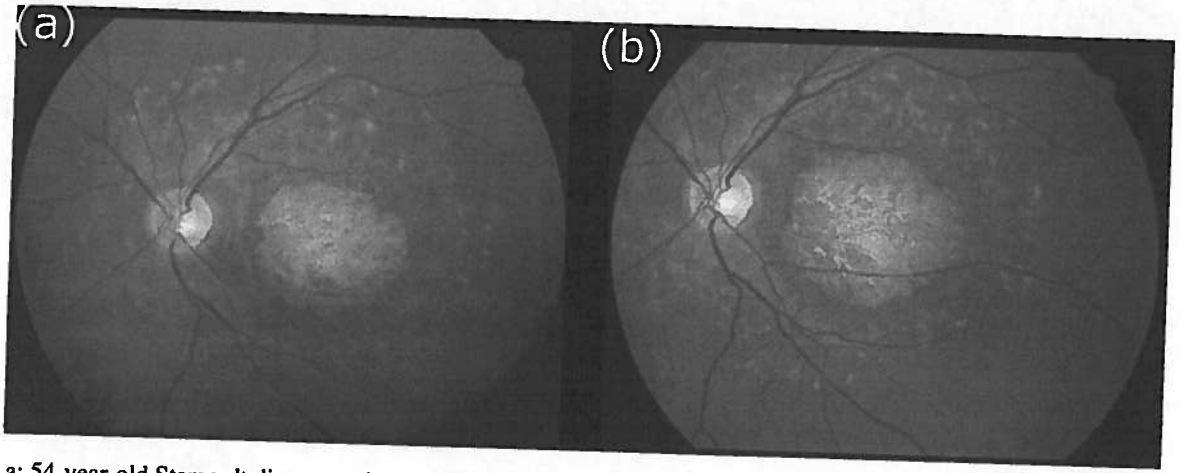

FIG. 5. a: 54-year-old Stargardt disease patient with a macular atrophic lesion and visual acuity of 20/200. b: Same patient at the age of 58 years, with an increase in size of the atrophic macular lesion, visual acuity of 10/120.

and finally photoreceptor degeneration. The phenotypic variability seen in Stargardt disease is due to a different extent of lipofuscin accumulation and RPE/photoreceptor degeneration in different parts of the retina. These authors have also postulated that slowing of the retinoid cycle kinetics may not be seen in all patients, and, if present, the level of slowing is not homogenous across the retina, but depends upon the extent of retinal degeneration.[23]

We observed that Stargardt patients with fundus foveal sparing can maintain good visual acuity for decades after an initial diagnosis. It has previously been shown that visual acuity in patients with Stargardt disease correlated with the extent of foveal macular pigment, which may impact upon the structural integrity of the foveal cones.[24] It has also been observed that visual acuity in patients with Stargardt disease negatively correlates with transverse photoreceptor loss and central foveal thickness, as measured by ultrahigh-resolution optical coherence tomography.[25]

The clinical findings described in this article are important for counseling patients with Stargardt macular dystrophy. These findings are also of interest for monitoring patients with foveal or relative foveolar sparing during future treatment trials. Visual prognosis will likely be more favorable in patients who first present at a later age (>20 years); who initially present with stage 1 disease or those who have fundus foveal sparing on clinical examination. For most patients with Stargardt disease, visual acuity declines to 20/200 or 20/400 and then tends to stabilize.

ACKNOWLEDGMENTS

Acknowledgments This work was supported by funds from the Foundation Fighting Blindness, Owings Mills Maryland, USA; the Grant Healthcare Foundation, Lake Forest, Illinois, USA; NIH core grant YO 1792, and an unrestricted departmental grant from Research to Prevent Blindness.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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#1- NEER 2011 Steering Committee Mtg Minutes

NNRI NEER Steering Committee

June 20, 2011, Columbia, MD, 9 AM – 4 PM

Attendance: Steven Bramer, Ph.D., Stephen Rose, Ph.D., Brian Mansfield, Ph.D., Amy Laster, Ph.D., Morton Goldberg, MD, Jerry Cagle, Ph.D., David Brint, Judith Chiostri, Jennifer McCormack, Col. Donald Gagliano, MD, Igor Kozak, MD, PhD, Marco Zarbin, MD, PhD, Jean Bennett, MD, PhD, Paul Bernstein, MD, PhD, Donald Zack, MD, PhD, Hendrik Scholl, MD

Opening Comments:
NNRI's Chief Drug Development Officer Dr. Steven Bramer opened the meeting with a welcome to the Committee and provided them an overview of the agenda and reviewed the goals for the day. Dr. Bramer also provided a brief synopsis of joint NNRI and NEER activities to date for those individuals who have not participated previously in NEER Committee discussions.

Upcoming Opportunities:
Dr. Bramer briefly presented several products that are being considered for further investigation within the NEER network, including deuterated vitamin A (Alkeus), Channel rhodopsin 2 (RetroSense), and fenretinide (ReVision). Additional molecules will be considered as they are identified. NNRI's main criteria for assessing opportunities include: 1) clearly defined ownership of the intellectual property (IP), 2) established freedom to operate, and 3) a thorough safety assessment (is it going to cause harm?). Research on repurposing existing molecules already in use has the additional benefit of providing a more extensive safety history. While the cure of retinal degenerative diseases is the ultimate goal, NNRI is working in the interim to identify preventions and treatments to slow the progression of retinal degenerations.

Dr. Bramer noted that NNRI is also cognizant of the Food and Drug Administration (FDA) requirements when planning a clinical research trial or development program. NNRI has maintained close communication with the FDA and had met with Dr. Wiley Chambers of the FDA earlier this spring. Dr. Chambers' guidance included the following information: 1) the rules for FDA drug approval are not different for orphan diseases than other populations, 2) diseases with very limited number of people afflicted does not change the requirements for a properly powered study to test for a statistically and clinically meaningful difference. If the test product has remarkable efficacy the sponsor should be able to test the hypothesis in a small population of patients. 3) endpoints should be well-defined and precise, and 4) studies should be planned to remove as much 'noise' (factors that may make interpretation of the data difficult), as possible.

If a pivotal study is planned, the committee members agreed obtaining FDA input is a prudent strategy. It was noted that FDA has allowed consideration of the results from studies conducted outside the USA provided one can show the practice of medicine is similar to the USA and there are not any intrinsic or extrinsic factors that would lead to different clinical response to therapy

in the various regions of the world. Study benchmarks should be the same, whether foreign or domestically conducted.

Examples of products and projects that were considered by NNRI but did not move forward included:

1) Investigator Kris Palczewski from Case Western University has a new investigational product. To date, an agreement by Dr. Palczewski to share proprietary information with NNRI/NEER has not been reached.

2) QLT, a company located in Canada, would like to include RPE65 genetic mutations in their study of their retinoid treatment that has shown potential efficacy in LRAT LCA. QLT and NNRI are in discussions on how to proceed in a partnership for this.

3) There was further discussion regarding indentifying domestic and foreign resources for appropriate study populations and funding for ultra orphan diseases. An example of a foreign collaboration discussed was King Khalid Eye Specialist Hospital (KKESH) in Saudi Arabia and the Wilmer Eye Institute at the Johns Hopkins University. It was agreed there are special considerations, in regard to Middle East politics, to think about before NEER would engage in recruiting clinical trial participants from these centers. NNRI continues to investigate opportunities for interventions and recruitment as they arise.

<u>EMMES Study Management Processes:</u>
Jennifer McCormack provided an overview of the services EMMES provides to NNRI as the Clinical Coordinating Center (CCC). EMMES has over 30 years of experience including government contracts with NEI (specifically, AREDS I and II and the ECT-CNTF phase I clinical trial). EMMES' initial start up support of the NEER network since 2008 has included establishment of Network policies, an online system for submission and review of proposals, and a NEER network web site. EMMES has also conducted site establishment visits with several of the NEER network sites, and is involved with statistical and clinical study design.

With the onset of the VPA trial in 2010, EMMES' support expanded into clinical trial protocol development and development of protocol related documents such as manuals of operations, electronic case report forms, study logs and worksheets. EMMES is preparing the statistical analysis plan and has implemented interim data reporting. They provide regulatory support, collect data through electronic data capture system, drug accountability utilities, safety oversight, clinical site monitoring and they partner with the OHSU Clinical Trial Reading Center to help manage and resolve technical issues. EMMES provides training to clinical sites via webcasts, bi-weekly teleconferences, and the NEER Network website. Ms. McCormack summarized that communication is the key to the success of the trial.

A question was posed about ownership of the electronic data capture system designed by EMMES. It is proprietary software owned by EMMES. If NNRI decides not to continue contracting with EMMES for CCC services, NNRI would need to build an electronic data capture system, which includes in-house IT (e.g., dedicated servers and software), electronic case report

forms (eCRF) development, security to meet FDA requirements, and other infrastructure to provide the level of support needed to conduct a clinical trial. In addition, NNRI would require dedicated statistical expertise for protocol development and clinical trial results analysis as well as administrative support for the Data Safety and Monitoring Board and the interactions with the Reading Center at OHSU.

A suggestion from the committee was made for NNRI and EMMES to communicate more effectively with the scientific community about the VPA trial and emphasize the excellent safeguards being put into place.

VPA Trial:

Introductory information was presented by Dr. Bramer regarding the initial selection of VPA as the NEER network's first drug to be investigated in the NEER network. FFB/NNRI felt a scientific answer whether or not VPA was effective in RP and to identify which genetic mutations that would benefit from VPA use was needed considering all the individuals being treated off-label for various retinal degenerations, including all forms of RP.

Dr. Paul Bernstein, Principal Investigator of the NEER Network clinical site at Moran Eye Center, University of Utah, gave a presentation concerning VPA and the activities of the VPA clinical trial to date. The presentation included overviews of the drug and its possible side effects, the possible mechanisms of action, and background information regarding the off-label use by Dr. Shalesh Kaushal. Dr. Bernstein reviewed the basics of the trial design, inclusion and exclusion criteria, genotype qualification, and the assessments at each in-clinic visit. He reported on recruitment and enrollment efforts to date for Moran and the Retina Foundation of the Southwest; he also reported satisfaction with the turnaround time for genetic testing by GeneDx, which has typically been about one month.

There was discussion regarding the assessments at in-clinic visits specifically regarding reported exhaustion experienced by both patients and technicians during the one-day testing schedule. It was suggested that a two-day testing schedule be considered; either two consecutive days or two days within the same week would be acceptable. Dr. Bramer noted he would prepare an estimate on the cost impact of allowing two-day clinic visits and would take that information as well as the recommendation to the NNRI Board.

Dr. Bernstein made a suggestion that he would prefer to see visual fields measured again at 65 weeks but there was no support for making this change in the protocol at this time.

There was discussion on the presumed action of the drug in ADRP patients on mis-folded proteins and whether the selection of patients for the trial should be based on the identification of subjects that specifically carry a genetic mutation for mis-folded proteins. It was noted that mis-folding may not be the only action of VPA. Genetic testing and screen failures due to not finding a subject's genetic mutation in the Tier 1 ADRP testing by GeneDx was discussed; specifically whether or not to include Tier 2 and/or Tier 3 testing to try to capture additional confirmed ADRP patients. Dr. Bernstein stated, based on his experience showing clear ADRP inheritance patterns, that he felt current recruitment guidelines for genetic

testing were allowing some ADRP subjects to be missed. It was recommended that NNRI consider allowing additional genetic testing if Tier 1 did not return a positive ADRP mutation identification and clinical records strongly support a dominant inheritance pattern. Dr. Bramer will prepare a budget and take the recommendation to the NNRI Board.

Dr. Bernstein reported on a glitch with the Octopus 900 software that had been identified by both clinical sites. The software timed out near the end of the testing and all data gathered at that point for that subject was lost. Testing had to be restarted from the beginning. It was reported to the manufacturer who acknowledged the glitch but gave no further support; EMMES is also aware of the issue and is working with the Oregon Reading Center and Haag-Streit to resolve it.

Lessons Learned from VPA Trial Start-up:

What we did well:

- Developed document templates for study and future NEER use (contracts, protocols, etc.)
- Developed a good relationship with the Department of Defense's Human Research Protections Office (HRPO) representative that reviews our study documentation
- Developed good relationships with contractors (such as EMMES Corp. and the OHSU Reading Center), and equipment suppliers
- Established an engaged DSMB
- Stayed within budget for our contractors and equipment suppliers

Lessons learned for next trial:

- Human Research Protections Office (HRPO) review time of study/documents increases with each additional clinical site
- Be realistic in amount of time for HRPO review up-front
- Utilize the HRPO Guide for Investigators (released Sept 2010) carefully to reduce number of reviews
- Consider equipoise status of each PI prior to selecting a site for participation and enrollment in a clinical trial (*note, equipoise refers to the belief of an investigator that none of the potential treatments used in a clinical trial necessarily offers superior treatment and the investigator may therefore ethically, and without bias, randomize subjects to any of the treatments*)
- NNRI or a company should hold the project IND, not individuals participating in the trial.

TUDCA Trial:

Dr. Steven Bramer presented an in-depth analysis of the results of the recent NNRI study involving TUDCA dosing in three nonhuman primates. Investigations completed by Dr. Jeff Boatright (Emory University) involving UDCA in mouse models and by Dr. Penelope Hogarth (OHSU) in dosing humans with UDCA were discussed as related bridges in TUDCA development efforts. He presented the known similarities and differences between UDCA and TUDCA.

Dr. Bramer outlined a proposal for the next steps in the investigation of TUDCA as the next product for investigation under a clinical trial supported by NNRI and the NEER Network. It

would continue with a two-stage Phase 1 study: 1) first stage would investigate the pharmacokinetics of oral TUDA for tolerance and dosing in healthy volunteers, and 2) the second stage would involve dosing patients already slated for vitrectomies with TUDCA (dose to be determined in first stage study) prior to surgery and then verifying the presence of TUDCA in the plasma and vitreous. This could be followed with a Phase 2a clinical study to determine whether oral supplementation of TUDCA could be beneficial. Dr. Bramer proposed a 1 year observational study in order to characterize the subjects' rate of disease progression followed by a 2 year study involving up to 200 eligible participants at up to eight clinical centers.

Discussion followed the presentation regarding the dosage for humans, specifically 2000 vs. 4000 mg per day and how to extrapolate dosage for humans from animal studies, especially mouse studies. A 2000 mg dose of TUDCA has been previously used in a clinical trial for Amyotrophic Lateral Sclerosis and a 1750 mg dose for insulin resistance; it was noted that a clinical trial with TUDCA will require NNRI to file an IND application with the FDA.

Current UCSD Capabilities:

Dr. Igor Kozak presented an overview of the University of California, San Diego NEER clinical site under the direction of Dr. William Freeman (not able to be present at this meeting), specifying staffing, capabilities and technology. He summarized activities to date in preparation for natural history studies. There were questions and discussion by the committee regarding some of the technology in use at UCSD and comparisons of equipment available at other sites. Dr. Rose expressed an interest in the data being generated by the natural history study and will follow-up with Dr. Freeman and Dr. Kozak on details.

Stargardt's Disease:

Dr. Bramer recapped points from a recent meeting between NNRI and FDA discussing the study of Stargardt's disease, and its unknown progression rate. It's in the collective best interest of science and the NEER network to build a thoughtful, prospective research plan for controlling variables that would make interpretation of the study's results difficult. Selection of endpoints will be an item to specify with FDA's guidance; visual acuity and visual fields have typically been the standard acceptable endpoints. FDA appeared willing to accept OCT measurements as a possible outcome measure if there was compelling evidence results would correlate with a visual function measurement, e.g., either visual field or visual acuity. The FDA does see the utility for capturing OCT outcomes as a safety measure to monitor structural changes over time.

There was discussion on characterizing ideal subjects to enroll in a Stargardt's trial, such as mild to moderately affected subjects vs. moderate to severely affected subjects. It was also noted that past progression may not be the same as future progression and that the progression rate of Stargardt's is not the same in everyone. However, a run-in phase which includes assessments of disease progression following either a specified protocol or from documented, reliable/timely information from clinical records could possibly indicate a likelihood of progression as assessed by a masked expert.

Age for participation in a Stargardt's disease trial was discussed; specifically, whether or not to include those under the age of 18 years. Issues noted: 1) many minors and their parents would

likely be willing to participate in a clinical trial, 2) as many as 50% affected are missed if you don't include those under the age of 18, and 3) while Stargardt's lends itself to a pediatric population study, the risk should be assessed in an adult population prior to treating the pediatric population.

Final Discussions:

Suggestions for Future NEER Network Activities from the Committee Members:

- A Foundation Fighting Blindness (FFB) sponsored traveling bus to assist in gathering data for natural history studies. The bus would make yearly visits to specific sites around the US, to follow participants.
- Become involved in iPS cells and screening devices for future activity in looking at cell cultures for genotyped Retinal Degenerative Diseases (RDDs).
- Explore possible opportunities to work with Dr. Don Zack and the National Chemical Genomic Center.
- Explore how to get DOD centers involved, possibly with recruitment.

The meeting closed at 4pm.

Action Items:

- A suggestion from the committee was made for NNRI and EMMES to communicate more effectively with the scientific community about the VPA trial and emphasize the excellent safeguards being put into place.

- It was recommended that NNRI consider allowing additional genetic testing in the VPA Study if Tier 1 did not return a positive ADRP mutation identification and clinical records strongly support a dominant inheritance pattern. Dr. Bramer will prepare a budget and take the recommendation to the NNRI Board.

- It was suggested that a two-day VPA study testing schedule be considered; either two consecutive days or two days within the same week would be acceptable. Dr. Bramer noted he would prepare an estimate on the cost impact of allowing two-day clinic visits and would take that information as well as the recommendation to the NNRI Board. (Post meeting note: the NNRI Board has approved expenditures for reimbursement of travel expenses for subjects requiring 2 days to complete study visit assessments).

#2- UCSD CTEC Report

Title: **The National Neurovision Research Institute/Foundation Fighting Blindness Grant – Progress Report**

Contract number:	NNSP-CTEC-0309-0038-UCSD-NER
Funding period:	August 1, 2010 to July 30, 2011
Principal Investigator:	William R. Freeman, MD
Co-Investigators:	Igor Kozak, MD, PhD, Radha Ayyagari, PhD
Location:	University of California San Diego, Jacobs Retina Center

The attached following document is a summary of our experience and research in testing retinal structure and function in eyes with degenerative retinal diseases. These studies were carried out by Drs. Kozak, Freeman, Ayaagari and the UCSD Jacobs Retina Center staff and faculty and were supported, in part, by FFB funds. In order to facilitate review of this data, we have prepared a three-page summary of our findings and feel that this can be used by FFB to prepare a protocol to use appropriate techniques to follow-up retinal degeneration patients. We have categorized testing of retinal degenerations into function and structure categories.

Section 1

INTRODUCTION

The FFB in collaboration with the National Neurovision Research Institute (NNRI) has been interested in the study of inherited orphan retinal degenerative diseases and dry and dry age-related macular degeneration. The UCSD participation in this project (from Contract between the NNRI and the Regents of the UCSD Article I, items #2 on page 4 as of 08/01/2009) has been to study:

1. *Phase I and II clinical trials to evaluate the safety and efficacy of investigational therapeutic and preventive interventions, including devices, biopharmaceuticals, small molecules, nutritional supplements, delivery systems, and gene transfer approaches.*

   NNRI has started a clinical trial of valproic acid for autosomal dominant retinitis pigmentosa. In conjunction with our collaborators, Dr. Ferreyra and Dr. Ayyagari, we determined that we have a small number of patients for participation. This is a difficult trial because autosomal dominant retinitis pigmentosa with the mutation needed is rare. The UCSD site has been inspected and approved for this trial by NNRI/NEER Network on June 30, 2011. It has not been determined if there are sufficient patients to bring us in as a center but we did offer to be a center for San Diego, Orange County and Imperial County.

2. *Natural history of these diseases to develop standardized criteria to define disease stage, severity and progression.*

   Our center has started the use of multiple instruments to document retinal function and structure. These include color fundus photography, red-free and infrared imaging, SLO/microperimetry, Roland mfERG, spectral SLO/OCT, fundus autofluorescence and software to quantitate geographic atrophy area, loss of RPE and drusen volume secondary to retinal degeneration. We have begun to test a new device, the Vimetrix. The attached report is accompanied by a 3-page

structure and function "Summary Points" which describes our experience in testing these instruments and our recommendations for uses in clinical trials to be performed in retinal degeneration and dry AMD by NNRI. For each instrument we describe advantages and disadvantages. Please see Summary Points below, studies B.2 to B4.

3. *Observational studies to enhance understanding of the natural history of inherited orphan retinal degenerative diseases and dry AMD for different genotypes and phenotypes.*

   Our center is still developing a database and long-term follow-up of retinitis pigmentosa patients. In dry AMD we now have a cohort of 350 patients including drusen and geographic atrophy. Please see Summary Points below, studies A2, B2, B5.

4. *Evaluations of the reliability and validity of different treatment outcome measures available to determine those that are most appropriate for various genotypes as well as for specific interventions.*

   Please see Summary Points below, studies A1 to A5, B1, B5 and B6.

5. *The development of standard protocols for data collection for use in multiple studies.*

   Our "Summary Points" lists advantages and disadvantages of numerous functional and structural measure of testing for retinal disease.

6. *The establishment and maintenance of patient databases, classified by genotype and phenotype, to allow for the timely identification of eligible patients and to facilitate patients across for participation in clinical trials for specific genotypes and phenotypes; and the provision of access to unidentifiable patient data to NNRI.*

   We have a database of patients with retinal dystrophies with both genotypic and phenotypic classification who are potential study subjects. In the current grant

period, we have characterized the phenotype of 10 patients with recessive retinal distrophy using complete ophthalmic evaluation, fundus photography, fluorescein angiography and spectral OCT. Blood samples were collected from all patients and relevant family members. DNA was isolated from lymphocytes and genetic analysis was carried out in two steps. Initially, probands were screened for common mutations in known retinal disease genes. Patients with no mutations in known genes were further analyzed by sequencing their exome.

Blood samples collected from 6 patients were analyzed in this grant cycle. Initial analysis did not reveal the presence of mutations in known genes. Exome of three patients was captured using Nimblegen V2 probes and sequenced using a Illumina HiSeq machine. Currently analysis of the exome sequence is in progress to identify mutations associated with the retinal degeneration observed in these patients.

7. *In collaboration with NNRI and DOD, the design and conduct of short-term training programs for military ophthalmologists in the latest technologies and diagnostic and treatment regimens.*

Ophthalmology resident physicians from Balboa Navy Hospital in San Diego participate at the UCSD Department of Ophthalmology conferences. The Naval Hospital Balboa has access to our facility but a formal collaboration has not yet been requested by NNRI or DOD.

Section 2

SUMMARY POINTS

A. FUNCTIONAL STUDIES

1. Multifocal ERG

It is extremely difficult to evaluate latencies and amplitudes from both the first order and second order kernel multifocal ERG waveforms manually. Advanced statistical techniques can be reliably used to analyze this complex information. The electrode type and placement cause great variations in the recordings so that this must be carefully standardized and repeated control patients are required to help standardize the instrument. An additional problem with the mfERG is that the hexagons used across the approximately central 30 degrees of the retina are quite large (approx. one disc diameter on the retina or 78 degrees) and are, therefore, not expected to be sensitive to relatively slowly progressing retinal dystrophies including dry AMD or geographic atrophy.

Advantages: objective measure of retinal function

Disadvantages: need for standardization, difficult evaluation, sensitivity issues in follow-up of small lesions

2. SLO Microperimetry in dry AMD

The scanning laser ophthalmoscope microperimetry is able to detect changes in retinal sensitivity in AMD patients overlying drusen and at the margin of geographic atrophy. It is a useful device to grade focal retinal sensitivity in patients with dry AMD. The microperimetry is highly associated with imaging results. It is our impression that the microperimetry cannot be reliably used to image retinal sensitivity in areas as small as 125 microns or less.

Advantages: good sensitivity to detect decreased function over larger lesions

Disadvantages: sensitivity issues in follow-up of small lesions

3. Visual Field Analysis

In a clinical trial of a therapy of patients with retinal degenerations, it may be particularly important to have repeated visual fields performed. Unlike humans, the machine learning classifiers technique is able to detect trends of change more robustly if there are multiple fields done. This makes statistical analysis much more robust and helps offset the inherent variability of visual field testing. We also stress that there is a significant learning curve in visual field testing and one cannot reliably use a visual field until the patient has been tested twice. Thus each eye must be tested and only the third test (second session) may be reliable. If this is not done, one will have an artifact leading to improvement in visual field performance due to the practice effect; such an effect can confound a therapeutic clinical trial easily.

Advantages: good measure of functional follow-up

Disadvantages: subject dependent with learning curve, evaluation of fine changes may require advanced statistical techniques

4. Visual Function and Driving Ability

Driving simulator could be of value in testing retinal degeneration subjects in a clinical trial. Certainly a positive result of a therapeutic that is confirmed by improved driving ability would be an important result. There is one caveat however; with certain simulators, a significant percentage of individuals become nauseous while performing this visual evaluative driving test. This needs to be accounted for if this is going to be used as a clinical trial measure. There is also a practice effect so in a longitudinal study, this test must be administered 2-3 times prior to beginning the therapeutic trial.

Advantages: practical retinal function assessment

Disadvantages: influence of cognition on performance, difficulty performing test in some patients, further testing is required

5. Automated measuring of visual acuity, contrast and functional visual acuity with a novel computer system

The Vimetrics device is designed to reproducibly measure glare, ETDRS vision and contrast sensitivity in a semi automated way to allow evaluation of vision in all types of

light conditions. This may be a very useful modality to evaluate patients with retinal degenerations and since the instrument is automated it may be useful in clinical trials of retinitis pigmentosa patients and AMD patients.

Advantages: fully automated vision assessment system, FDA approved

Disadvantages: still needs validation in different diseases, ongoing work

B. STRUCTURAL STUDIES

1. Automated Quantification of GA Progression

We have worked with Heidelberg Engineering on developing the retinal degeneration software to provide semi-automatic quantification of atrophic areas seen by SLO autofluoresence by a semi-automatic quantification of well-demarcated regions with significantly decreased autofluorescence intensity seen by blue laser autofluorescence.

Advantages: an easy and reliable assessment of retinal atrophy

Disadvantages: still needs validation, ongoing work

2. Effect of change in drusen evolution on photoreceptor inner segment/outer segment junction (natural history)

Raster scanning using high quality SD-OCT does permit observation of the evolution of drusen. Approximately 20% of drusen regress over a median time of two years, 51% appear stable and the remaining increase in size. The SD OCT observed progression of drusen causes a damage of the IS/OS-junction.

Advantages: description of natural history of drusen by reproducible high-resolution technology

Disadvantages: needs development of new software to be used in analysis of more robust data

3. OCT-raster scanning and manual segmentation in determining drusen volume in dry AMD

The SD OCT can quantify abnormal and normal retinal and RPE tissue. Drusen volume, as determined by spectral domain-OCT, correlates with AREDS-determined drusen area

and AREDS grade in dry AMD. Drusen volume can provide additional information in grading the severity of eyes with dry AMD.

Advantages: quantitation of disease burned in the retina by reproducible high-resolution technology

Disadvantages: image detection and algorithm analysis needed, ongoing work

4. Long-term SD-OCT/SLO imaging of neuroretina and retinal pigment epithelium after subthreshold infrared laser treatment of drusen

Subthreshold diode laser treatment causes long-term disruption of the retinal photoreceptor layer as analyzed by spectral domain optical coherence tomography/scanning laser ophthalmoscope. The concept that sub-threshold laser treatment can achieve a selected retinal pigment epithelium effect without damage to rods and cones may be flawed. SD OCT clearly can detect subtle RPE changes in many types of retinal degenerations.

Advantages: detection of long-term damage by reproducible high-resolution technology

Disadvantages: image detection and algorithm analysis needed, ongoing work

5. Correlation between spectral-domain optical coherence tomography and fundus autofluorescence at the margins of geographic atrophy

Spectral-domain OCT provides in vivo insight into the pathogenesis of geographic atrophy and its progression. It enables visualization of reactive changes in the RPE cells at the junctional zone and correlation with increased FAF; secondary to increased lipofuscin. Together these methods may serve as determinants of progression of geographic atrophy. Indeed it is likely that SD OCT is as good a predictor as FAF and also can be used to determine lesion size.

Advantages: Spectral OCT technology correlates well with fundus autofluorescence and can be used in clinical trials as a tool to assess disease progression

Disadvantages: need of multiple scans in one session

6. The association between percent disruption of the photoreceptor inner segment-outer segment junction and visual acuity

The disruption of the photoreceptor IS/OS junction is an important predictor of visual acuity among macular edema patients. Also, disruption of the photoreceptor IS/OS junction is a statistically significant predictor of poor visual acuity among patients with ERM, and is most useful when combined with central retinal thickness measurement. Certainly evaluation of the photoreceptor IS/OS junction should be a part of imaging studies in retinal degenerations.

Advantages: excellent measure of structure-function correlations, can be used in clinical trials as a predictor of vision loss

Disadvantages: requires high quality scans and an experienced evaluator. Software for automated detection in raster scans under development.

Section 3

Retinal functional analysis and imaging in degenerative diseases

The current report is divided into retinal functional analysis followed by retinal imaging studies

PART I: FUNCTION

A. MF-ERG as a measure of retinal function in retinal disease and degenerations

We use the Roland multifocal ERG device and we have performed a total of 560 examinations using contact jet electrodes in conjunction with the DTL electrodes. This includes a group of 30 age-matched normals and 80 patients in a psychology cohort with no ocular disease. Of interest to NEER is that we have studied 200 patients with HIV retinopathy, 10 with suspected macular toxicity and approximately 10 with forms of hereditary retinal degenerations.

Electroretinography is a standard method for measuring retinal dysfunction in widespread retinal disease but is notoriously difficult to standardize and is not sensitive to small change either ring area or magnitude. For this reason, multifocal (mf) ERG has become a more recent tool that is used. We have been interested in studying relatively subtle but widespread retinal dysfunction in HIV patients with out retinitis and have published several studies of interest to FFB. We use the Roland multifocal ERG because it has the advantage of being able to be fitted to a scanning laser ophthalmoscope.

Analysis with support vector machine shows HIV-positive subjects without infectious retinitis have mfERG deficiencies compared to normal eyes. This was a fairly large study comprising 206 eyes, which also had collected visual acuity data, visual field, contrast sensitivity and other data. We hypothesized that (1) eyes from individuals with human immunodeficiency virus (HIV) have electrophysiologic abnormalities that

manifest as multifocal electroretinogram (mfERG) abnormalities; (2) the retinal effects of HIV in immune-competent HIV individuals differ from the effects in immune-incompetent HIV individuals; (3) strong machine learning classifiers (MLCs), like support vector machine (SVM), can learn to use mfERG abnormalities in the second-order kernel (SOK) to distinguish HIV from normal eyes; and (4) the mfERG abnormalities fall into patterns that can be discerned by MLCs. We applied a supervised MLC, SVM, to determine if mfERGs in eyes from patients with HIV differ from mfERGs in HIV-negative controls. We topographically analyzed the amplitude and latency of the first positive curve (P1, hereafter referred to as 'a') and the first negative curve (N1, referred to as 'b') in the SOK of 103 hexagon patterns of the central 28 degrees of the retina were recorded from the eyes in each group. SVM was trained and tested with cross-validation to distinguish H from N and L from N. SOK was chosen as a presumed detector of inner retinal abnormalities. Classifier performance was measured with the area under the receiver operating characteristic (AUROC) curve to permit comparison of MLCs. Improvement in performance and identification of subsets of the most important features were sought with feature selection by backward elimination. We found that, in general, the SOK b-parameters separated L from N and H from N better than a-parameters, and latency separated L from N and H from N better than amplitude. In the HIV groups, on average, amplitude was diminished and latency was extended. The parameter that most consistently separated L from N and H from N was b-latency. With b-latency, SVM learned to distinguish L from N (AUROC = 0.7.30 +/- 0.044, P = .001 against chance [0.500 +/- 0.051]) and H from N (0.732 +/- 0.038, P = .0001 against chance) equally well. With best-performing subsets (21 out of 103 hexagons) derived by backward elimination, SVM distinguished L from N (0.869 +/- 0.030, P < .00005 against chance) and H from N (0.859 +/- 0.029, P <.00005 against chance) better than SVM with the full set of hexagons. Mapping the top 10 hexagon locations for L versus N and H versus N produced no apparent pattern. This study shows the ability to analyze complex topographically mapped mfERG data, and confirms that mfERG SOK abnormalities develop in the retina of HIV-positive individuals. SOKs are difficult for human experts to interpret. Machine learning classifiers, such as SVM, learn from the data without human intervention, reducing the need to rely on human skills to interpret this test. We

stress however that such complex acquisition and analytical techniques may be difficult to incorporate into a multi-centered clinical trial of a focal retinal degeneration; they may be applicable to widespread degeneration long-term treatment studies, but the methods must be extremely and carefully standardized and instruments carefully calibrated. **Goldbaum MH, Falkenstein I, Kozak I, Hao J, Bartsch DU, Sejnowski T, Freeman WR: Trans Am Ophthalmol Soc. 2008;106:196-204; discussion 204-5.**

SUMMARY

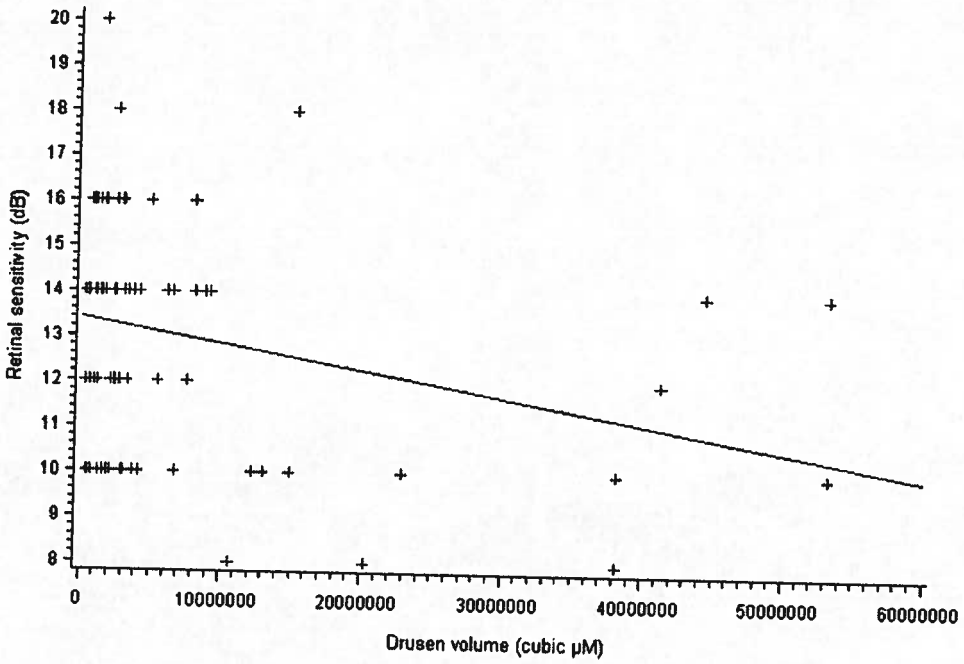
We have studied the use of mfERG in patients with inner retinal damage due to HIV disease. We have studied both the first order and second order kernel waveforms including the equivalent of latencies and amplitudes. We have found it extremely difficult to evaluate these tracings manually and feel that only advanced statistical techniques can be reliably used to analyze this complex information. We have also found that electrode type and placement cause great variations in the recordings, so that this must be carefully standardized and repeated control patients are required to help standardize the instrument. An additional problem with the technique is that the hexagons used across the approximate central 30 degrees of the retina are quite large (approximately one disc diameter on the retina or 78 degrees) and are, therefore, not expected to be sensitive to relatively slowly progressing retinal dystrophies including dry AMD or geographic atrophy. We have found that studying this data can be done potentially more reliably by using artificial intelligence technology.

B. Additional Functional Evaluation of the retina with SLO-Micro-Perimetry

Another important approach to evaluating vision function, particularly in focal atrophic retinal diseases such as Stargardt's disease, geographic atrophy, dry AMD and certain types of retinal degenerations is the use of microperimetry. We evaluated a unique instrument, the OPKO SLO microperimeter which employs fundus image stabilization and permits microperimetry on an SLO image (infrared) of the living human eye. We found that we were able to map very small areas of macular and posterior pole retinal dysfunction. We performed studies in eyes with geographic atrophy, normal eyes, wet AMD and eyes with drusen to assess the value and utility of these instruments. In one of our papers in RETINA (**Hartmann KI, Bartsch DU, Cheng L, Kim JS, Gomez ML,**

Klein H, Freeman WR. Scanning Laser Ophthalmoscope Imaging Stabilized Microperimetry in Dry Age-Related Macular Degeneration. Retina 2011;31(7):1323-1331), we determined the effect of drusen and geographic atrophy (GA) in dry age-related macular degeneration on retinal sensitivity using this SLO microperimetry device. We studied 46 eyes including eyes with dry AMD and drusen as well as with geographic atrophy. Over 30 control eyes were also used to validate the instrument and assess normal values. A custom microperimetry pattern was used to evaluate retinal sensitivity to a Goldmann III size target (108 μm on the retina). The perimetry used a 4-2 step ladder algorithm to determine maximal sensitivity. Microperimetry and optical coherence tomography were performed using a standardized protocol. 28 eyes with drusen and 16 eyes with GA were analyzed. We found that retinal sensitivity overlying drusen was significantly reduced compared with the adjacent uninvolved retina. There was a significant correlation between retinal sensitivity and drusen volume, as well as the grading of the photoreceptor inner segment/outer segment junction. In patients with GA, an absolute scotoma was confirmed and correlated precisely with AF and FA imaging which could be overlaid on the SLO microperimetric map. Retinal sensitivity at the margin of GA was significantly decreased compared with the adjacent uninvolved retina.

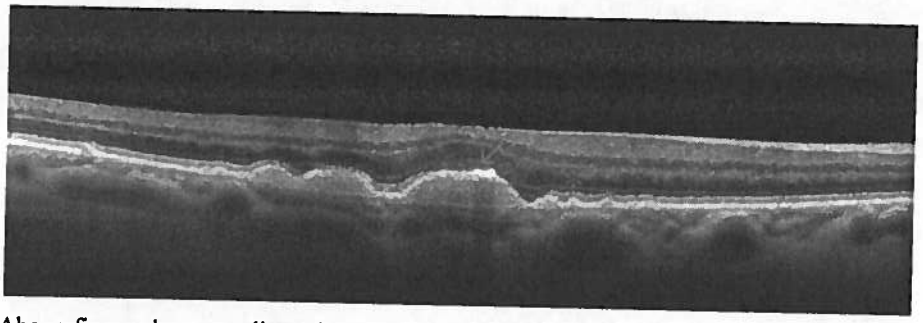
We also note several limitations that we discovered of microperimetry. Although attractive as a technique allowing measurement of focal retinal sensitivity, we found the reproducibility of the OPKO instrument (point to point) was only ± 4 Db. Since that instrument is on a scale of 20 db, this is not a high reproducibility value. In addition, because of micro-saccadic eye movements which are faster than the eye tracking rate of 8 Hertz on this instrument, small lesions may not be accurately stabilized for microperimetry.



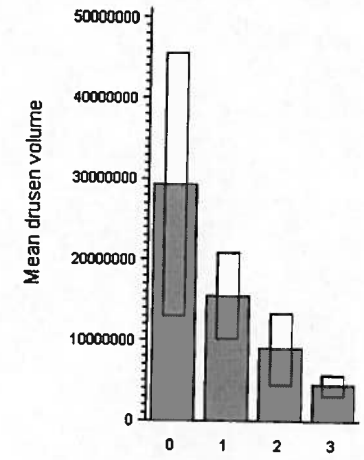
Above figure shows correlation of retinal sensitivity [dB] and drusen volume [μm^3] ($r = -0.339$, $p = 0.003$). The graph displays an inverse relationship between retinal sensitivity and drusen volume.

	drusen	adjacent retina	p-value
mean retinal sensitivity dB ± SD	12.96 ± 0.24	14.11 ± 0.39	0.0077

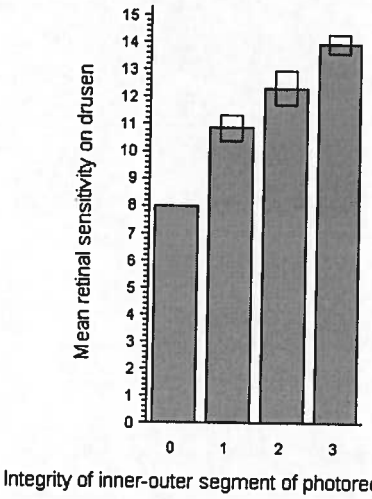
Above table shows decrease in retinal sensitivity over drusen versus uninvolved retina in the same area of the same eye.



Above figure shows grading of the IS/OS-junction integrity may demonstrate a complete disruption of the IS/OS junction over large drusen (arrow), whereas the integrity of the IS/OS junction was mostly intact above small drusen (asterix). IS/OS integrity correlates with retinal sensitivity.

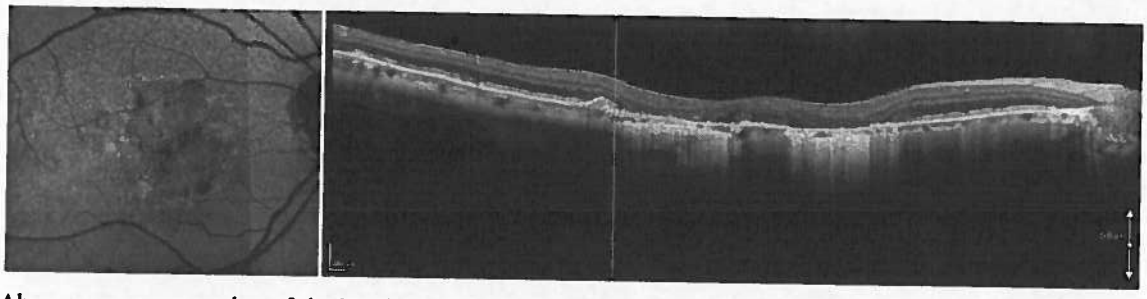


Left graph shows correlation of the Inner-outer segment integrity score above drusen and drusen volume ($r = -0.339$, $p = 0.003$).



Left we show correlation of the Inner-outer segment integrity score above drusen and retinal sensitivity ($r = 0.598$, $p < 0.001$).

Left is a color picture of a patient with GA (visual acuity 20/125). Retinal sensitivity was tested and SD-OCT was performed.



Above we see an overlay of the MP infrared picture onto the fundus autofluorescence. Right: SD-OCT of the same eye. The circle on the MP shows the same point visualized on SD-OCT as marked by the green line. This shows the ability to localize lesions with fundus photographs and microperimetry.

SUMMARY

This study shows that scanning laser ophthalmoscope microperimetry is able to detect changes in retinal sensitivity in AMD patients overlying drusen and at the margin of GA. It is a useful device to grade focal retinal sensitivity in patients with dry age-related macular degeneration. The microperimetry is highly associated with imaging results. It is our impression that the microperimetry cannot be reliably used to image retinal sensitivity in areas as small as 125 microns or less.

C. Use of Artificial Intelligence to analyze visual field loss in diffuse progressive retinal disease

In any analysis of visual fields in slowly progressing degenerations, one must also recognize that human observers may be relatively insensitive to change and progression, and we have shown that machine learning (artificial intelligence) may be a more robust way to evaluate multiple topographically-localized subtle visual field defects which are difficult to see by the human observer, and which may not be apparent with standard Humphrey analysis techniques. We published an important paper evaluating this: **Goldbaum MH, Kozak I, Hao J, Sample PA, Lee T, Grant I, Freeman WR: Pattern recognition can detect subtle field defects in eyes of HIV individuals without retinitis under HAART. In Graefes Arch Clin Exp Ophthalmol. 2011;249(4):491-498.** In this study, we also used machine learning classifiers (MLCs) to seek differences in visual fields (VFs) between normal eyes and eyes of HIV+ patients; to find the effect of immunodeficiency on VFs and to compare the effectiveness of MLCs to commonly-used Statpac global indices in analyzing standard automated perimetry (SAP). We again studied high and low CD4 patients and age matched negative controls. A cohort of 130 patients was studied using a Humphrey Visual Field Analyzer, SAP full threshold program 24-2, and routine settings for evaluating VFs. We trained and tested support vector machine (SVM) machine learning classifiers to distinguish fields from normal subjects and high and CD4 groups separately. Receiver operating characteristic (ROC) curves measured the discrimination of each classifier, and areas under ROC were statistically compared.

We found that artificial learning using support vector machine learning could identify low CD4 HIV patients; the AUROC was 0.790 ± 0.042. SVM and MD each significantly differed from chance decision, with $p<0.00005$. High CD4 HIV patients: the SVM AUROC of 0.664 ± 0.047 and MD were each significantly better than chance ($p=0.041$, $p=0.05$ respectively). We therefore conclude that machine learning can be sued to study visual fields with great sensitivity but again has not been validated in multi-centered clinical trials. We found that eyes from both low and high CD4 HIV+ patients

have VFs defects indicating retinal damage; these techniques are effective at detecting HIV eyes that have field defects, even when these defects are subtle.

SUMMARY

We also note that in a clinical trial of a therapy of patients with retinal degenerations, it may be particularly important to have repeated visual fields performed. Unlike humans, the machine learning technique is able to detect trends of change more robustly if there are multiple fields done. This makes statistical analysis much more robust and helps offset the inherent variability of visual field testing as well as multifocal ERG testing. We also stress that we have found a significant learning curve in visual field testing and one cannot reliably use a visual field until the patient has been tested twice. Thus, each eye must be tested and only the third test (second session) may be reliable. If this is not done, one will have an artifact leading to improvement in visual field performance due to the practice effect; such an effect can confound a therapeutic clinical trial easily.

D. Driving Simulation

In our quest to evaluate meaningful functional measures of retinal performance, we also have evaluated several driving simulators. We performed testing in over sixty subjects on a one and three screen (wide angle) simulator. **(reference; Cheng S, Klein H, Bartsch D-U, Kozak I, Marcotte TD, Freeman WR: Relationship between Retinal Nerve Fiber Layer Thickness and Driving Ability in Patients with Human Immunodeficiency Virus Infection. Graefe's Archives, In Press).** A driving testing can be a test of vision or retinal function but also has non-visual components which must be controlled. We were able to validate the three screen instrument made by Systems Technology Corporation, Hawthorne, CA. We studied 38 patients including subjects with inner retinal disease due to HIV and appropriate controls. The wide field of view driving simulation included evaluations of missing traffic lights, off road excursions, crash avoidance. We found that HIV seropositive participants had a significantly higher weighted error score than control participants (18.4 [9.2] vs. 11.1 [4.5], p=0.006). NFL thickness was significantly correlated with driving errors ($r = -0.51$, $p = 0.025$); there was a trend for participants with a CD4 nadir < 100 to have more errors than those with a

nadir > 100 (29.7 [13.2] vs. 19.3 [8.4], p =0.056). The highest number of driving errors occurred in individuals with both CD4 < 100 and NFL thickness < 80. We conclude that there is a correlation between OCT measurements of RNFL thickness (structural evidence of retinal damage) and driving function.

SUMMARY

One may conclude that this type of driving simulator could be of value in testing retinal degeneration subjects in a clinical trial. Certainly a positive result of a therapeutic that is confirmed by improved driving ability would be an important result as it may be difficult for the Foundation for Fighting Blindness to demonstrate improvement and stabilization of peripheral retinal function in clinical trial. There is one caveat however; we found that a significant percentage of individuals become nauseous while performing this visual evaluative driving test. It appears that the disconnection between visual perception while looking at the monitor (central 30 to 70 degrees) produces a conflict between more peripheral visual perception (where nothing is moving) and vestibular perception (which also indicates to the brain that there is no real movement). This led to nausea and inability to complete the test in up to 20 percent of our subjects. This needs to be accounted for if it is going to be used as a clinical trial measure. There is also a practice effect, so in a longitudinal study, this test must be administered 2-3 times prior to beginning the therapeutic trial.

E. Automated measuring of visual acuity, contrast and functional visual acuity with a novel computer system to measure visual function

We have been evaluating an automated visual function device to allow testing of real world measures of vision in patients with macular disease and retinal degenerations. The Vimetrics device is designed to reproducibly measure glare, ETDRS vision and contrast sensitivity in a semi automated way to allow evaluation of vision in all types of light conditions. This may be a very useful modality to evaluate patients with retinal degenerations and since the instrument is automated it may be useful in clinical trials of RP patients and AMD patients. We studied a diverse group of 185 eyes with maculopathy including geographic atrophy and dry AMD with visual acuities between

20/16 and 20/300. Patients were tested on the instrument at 100%, 64% and 43% contrast, as well as under two glare conditions G2= 10% contrast with 80% off axis (vertical) source of light and G3= 8% contrast and 15 degree off axis (retro-illumination) conditions. We found (see curve below) that the Vimetrics does show that in eyes with atrophic macular disease, there is increasing dysfunction under back-light and dim light conditions. Reproducibility of the device was high. In diseased eyes with dry AMD, the concordance correlation (CCC) was between 0.82 and 0.90. Plots of ETDRS equivalent log MAR acuities under all five contrast conditions showed a decline in visual acuity as contrast lowered, and then further under additional glare/photo-stress conditions. The slope of the curve (worsening acuity with decreased contrast and additional photo stress) was higher in eyes with macular disease than in control non-diseased eyes by 50%.

SUMMARY

We believe an automated device such as the Vimetrics may be able to be validated and used as a way to quantitate vision in clinical trials of retinal degenerations (Gomez, ARVO 2011) to assess visual function under real life conditions.

PART II: STRUCTURE

A. Spectral-domain OCT (SD OCT) structural imaging

The following data, conclusions and statistics are based on examinations of 1,028 patients using simultaneous spectral OCT and scanning laser angiography using the Heidelberg Spectralis combination instrument. We studied 1,028 Patients of which 384 have AMD between January 2008 and June 2011 using standardized protocols.

1.1. Automated Quantification of GA progression

We have also just now begun to evaluate an automated algorithm for measuring lesion size in geographic atrophy. This new software has just been developed in conjunction with Heidelberg Engineering. It provides semi-automatic quantification of atrophic areas seen by SLO autofluoresence using quantification of well-demarcated regions with significantly decreased autofluorescence signal intensity seen by blue laser autofluorescence. The software has multiple functions. The first function is to interactively define regions of autofluorescence. The software allows us to select regions of interest and the signal intensity level will be used to automatically segment the image and determine the region of decreased autofluorescence. Blood vessels are automatically excluded from the analysis.

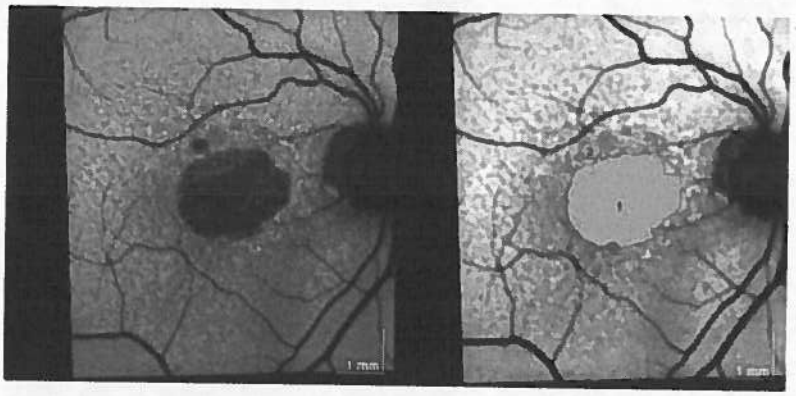


Fig. 16: Reading Results, 13 September 2007, OD

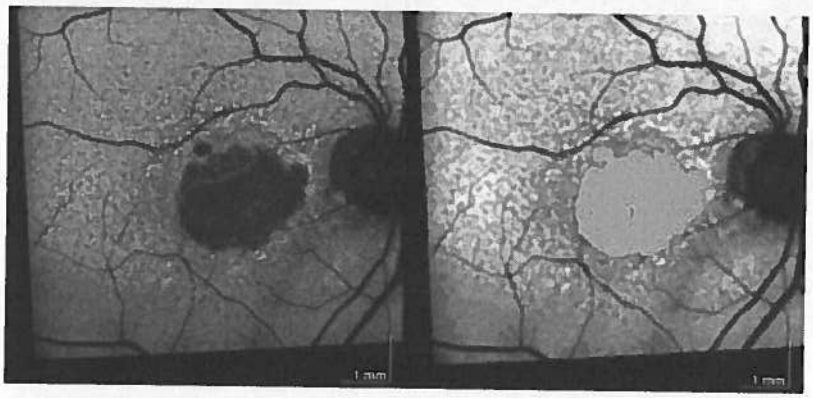


Fig. 17: Reading Results, 27 November 2008, OD

The montage above shows geographic atrophy progression and automated quantification in an eye with progressive vision loss.

The second function is the automatic process of including follow-up images in a series of blue autofluorescence images. This function ensures the precise re-definition of regions and constraints in all images of a follow-up series. All defined regions, corresponding parameters and constraints can be copied to subsequent images within a follow-up series. The subsequent image must be part of the same follow-up series. The image initially used to define the regions will now become the comparison image once the copy process has been completed. The report function allows a graphical printout of the total area of decreased autofluoresence, the change in area from prior reference and the rate of change.

SUMMARY

Geographic atrophy can be quantified using auto autofluorescence and progression objectively determined using blue light autofluorescence images.

1.2. Evaluation of SD-OCT as a substitute for F.A.

We have been interested to determine whether fluorescein angiography could be replaced in the evaluation of certain aspects of retinal degeneration research. We determined whether edema seen as fluorescein leakage could be seen by OCT with equal or greater sensitivity than fluorescein angiography **(Brar M, Yuson R, Kozak I, Mojana F, Cheng L, Bartsch DU, Oster SF and Freeman WR: Correlation Between Morphologic Features on Spectral-Domain Optical Coherence Tomography and Angiographic Leakage Patterns in Macular Edema. Retina. 2010;30:383–389).**

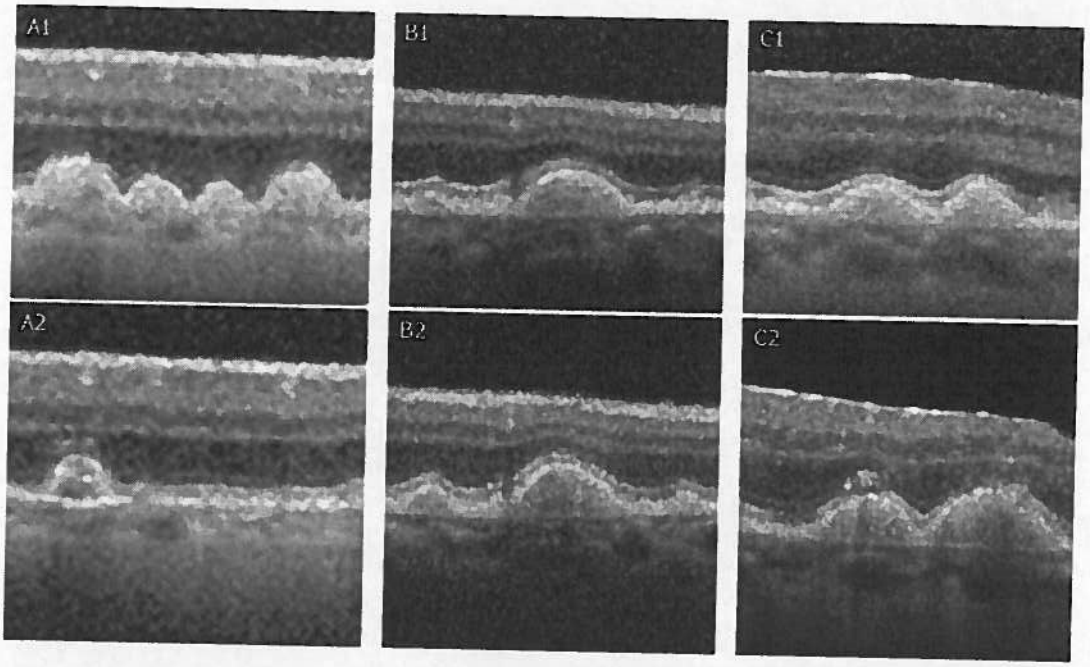
87 consecutive patients (107 eyes) with macular edema from 5 different etiologies were imaged by simultaneous scanning laser ophthalmoscopy/OCT to study the morphologic patterns of edema on SD-OCT, and then correlated/co-localized with the fluorescein angiographic patterns of leakage. Statistical analysis was done to analyze the differences in the morphologic OCT pattern by different diseases. Spectral-domain OCT characteristics of macular edema showed a significant difference across different diseases (P=0.037). Cystic fluid pockets were found to be more commonly seen in patients with diabetic macular edema and retinal vein occlusions, whereas, those cases with macular edema secondary to epiretinal membrane showed non-cystic changes on OCT. 70 of the 107 eyes had diffuse angiographic leakage, and the remaining 37 eyes had cystoid leakage on angiography. Of the 70 eyes with diffuse leakage, 24.28% showed microcysts on SD-OCT in the area of edema, and 70% eyes had diffuse thickening or distorted architecture without cyst. All 37 eyes with cystoid leakage showed cysts in the area of edema by SD-OCT. A total of 3.73% of eyes with fluorescein angiographic leakage had no abnormalities on SD-OCT. Eyes with diabetic macular edema and retinal vein occlusions have a significantly higher incidence of cyst formation on SD-OCT. There was no correlation between visual acuity and cyst formation. Diffuse non-cystoid angiographic macular edema may show microcysts on SD-OCT, but diffuse edema is more commonly associated with thickening or distortion of the retinal layers without cyst formation. Cystoid leakage on fluorescein angiography is always associated with cystic changes on SD-OCT.

SUMMARY

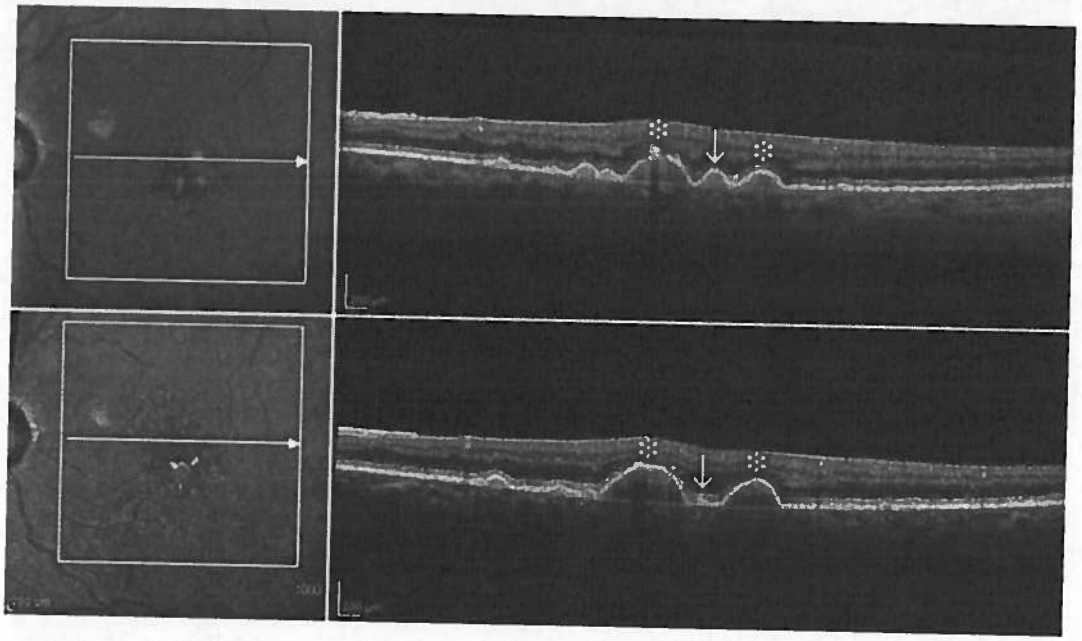
Fluorescence angiography may not be needed in clinical trials of retinal dystrophies or degenerations as edema and leakage seen on F.A. is usually also seen on SD-OCT.

1.3. The use of SD-OCT with image averaging and fundus tracking to study and quantify drusen and dry AMD

This paper is in press in the American Journal of Ophthalmology; **Ref: Hartmann KI, Gomez ML, Bartsch D-UG, Schuster AK and Freeman WR: Effect of change in drusen evolution on photoreceptor inner segment/outer segment junction.** We hypothesized that high quality SD OCT imaging could actually quantitate photoreceptor integrity because of the new found ability to quantiate the IS/OS junction reliably. This would be very helpful to include in clinical trials for retinal degenerative disease. For this reason, we determined our ability to evaluate the integrity of photoreceptor inner segment/outer segment (IS/OS) junction after change of drusen size in age-related macular degeneration (AMD), using spectral domain optical coherence tomography (SD-OCT). This was done by observing drusen evolution over a period averaging two years. Drusen volume raster scans were performed with the Spectralis SD-OCT(Heidelberg Engineering) through 2,624 drusen in 14 eyes with clinically dry AMD who had been longitudinally followed between 23-28 months without intervention (mean 26.3 months). All eyes had ETDRS visual acuity. We were able to analyze drusen evolution; of 416 drusen, 83 (20%) were found to have regressed spontaneously (group A), 212 (51%) showed no change in size (group B) and 121 (29%) progressed (group C), mean drusen size of all drusen was 63.7 ± 25.7 microns. Cross-sectional analysis of drusen morphology showed a strong correlation between drusen size and disrupted IS/OS junction/photoreceptor integrity ($p<0.005$). Of the drusen that regressed over time there was intact IS/OS junction integrity. Even drusen that caused a major disruption showed IS/OS restoration in 74% of the drusen ($p<0.001$).

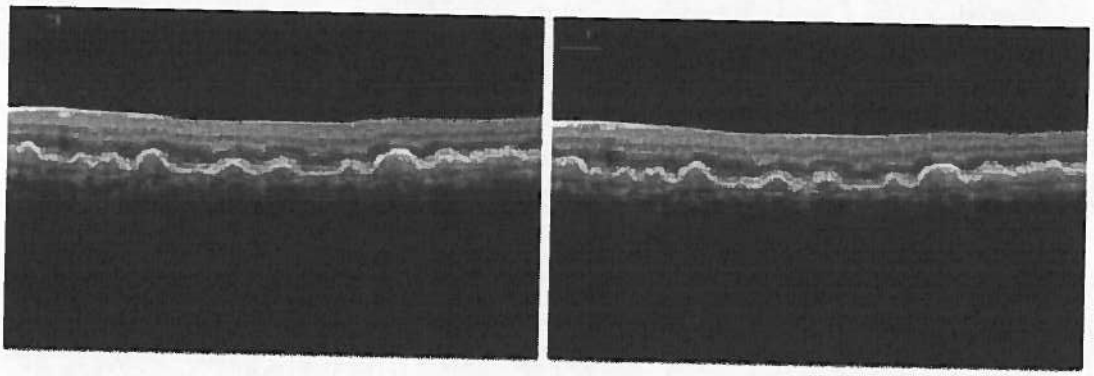


Above we show SD OCT in aged drusen at three tie points (upper row) and at a later visit (lower row); drusen regression/disappearance is seen in A, stable in B and progression in C.

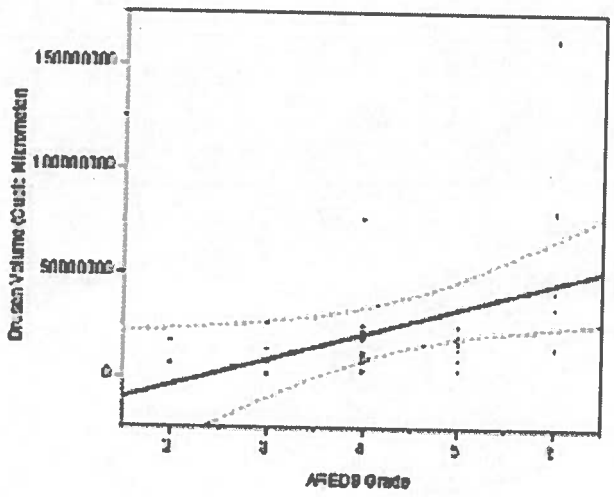


The figure above shows infrared (left) and SD OCT co localized drusen in areas that progressed (asterisk) and regressed (arrow). This eye demonstrates that the IS/OS junction gets disrupted with drusen growth. The location where the druse disappeared shows complete restoration of the IS/OS junction indicating that this disappearance (at least with drusen) could be a compression artifact.

We have also evaluated the ability of raster scanning SD OCT to allow quantification of abnormal subretinal material deposition in the form of drusen. The goal from FFB's perspective is to determine if closely spaced raster sans can permit quantification of retinal thickness, abnormalities under the retina or RPE area. This is a promising role of SD OCT and modern machines can scan so rapidly that in a few seconds 96 scans can be procured covering arcade to arcade for a length of 6 mm. We recently published this: **Freeman SR, Kozak I, Cheng L, Bartsch DU, Mojana F, Nigam N, Brar M, Yuson R, Freeman WR. Optical coherence tomography-raster scanning and manual segmentation in determining drusen volume in age-related macular degeneration. Retina. 2010;30(3):431-435.** Substantial evidence exists that the amount of drusen and their effect on retinal pigment epithelium is a strong predictor of progression of AMD and vision loss. Until recently, it was not possible to quantitate the volume of the drusen. However, the use of image-stabilized scanning laser ophthalmoscopy or spectral domain-optical coherence tomography (OCT) has enabled determination of drusen volume of this abnormal material. The purpose of this study was to assess the correlation of drusen volume with Age-Related Eye Disease Study (AREDS) grade and drusen area in dry AMD. We, therefore, studied 36 eyes from 18 patients with non-exudative AMD with visual acuity between 20/16 and 20/160. Spectral domain-OCT or simultaneous OCT scans were taken as color fundus photographs (35 degrees) of each eye. Early Treatment Diabetic Retinopathy Study visions were also recorded. The full AREDS score excluding late-stage AMD was determined by agreement between two trained observers. Drusen volume was determined by examination of a series of 96 spectral domain-OCT scans taken from arcade to arcade for a length of 6 mm. The volume was determined by calculating the drusen area in each scan, and determining the drusen volume by calculating the effective volume of each cut using National Institutes of Health Image J. Drusen were identified and outlined manually, not using an automated algorithm. We found that there was a strong and significant correlation between drusen volume and AREDS-determined drusen area ($P < 0.0001$, $r = 0.78$). In addition, there was a correlation between AREDS classification and drusen volume ($P = 0.023$, $r = 0.43$) as determined by pairwise correlation.



The above figure shows SD-OCT image of an eye with drusen. The drusen are well-defined deposits, which elevate the retinal pigment epithelium and neurosensory retina. The right image shows the manual method of determination of drusen volume. The yellow lines show the boundaries of the drusen. National Institutes of Health Image J software was used to determine drusen's cross-sectional area. In this image, two of the drusen had area determined for purpose of illustration.



Above we show Age-Related Eye Disease Study grade 1 to 6 (drusen description) on the x-axis is plotted against drusen volume performed by SD-OCT scanning.

SUMMARY

Closely spaced SD-OCT raster scans, if properly located and aligned with fundus images, can be used to quantify areas of drusen and geographic atrophy and potentially quantify photoreceptor damage. Further developments in automated segmentation software are required.

1.4. RPE Evaluation by SD/OCT

To further evaluate structural imaging of the retina as a marker of retinal degenerations, we studied RPE changes after sub-threshold diode laser burns. This is of importance to FFB because the study shows the ability of raster scanning SD OCT to image subtle changes and destruction of the pigment epithelium. The study was recently published; **Mojana F, Brar M, Cheng L, Bartsch DU, Freeman WR: Long-term SD-OCT/SLO imaging of neuroretina and retinal pigment epithelium after subthreshold infrared laser treatment of drusen. Retina. 2011;31(2):235-42.** Consecutive age-related macular degeneration patients with bilateral drusen previously treated with sub-threshold diode laser were imaged with spectral domain optical coherence tomography/scanning laser ophthalmoscope. Abnormalities in the outer retinal layers' reflectivity as seen with spectral domain optical coherence tomography/scanning laser ophthalmoscope were retrospectively analyzed and compared with color fundus pictures, and auto-fluorescence images were acquired immediately before and after the laser treatment. We found that a focal discrete disruption in the reflectivity of the outer retinal layers was noted in 29% of the laser lesions. The junction inbetween the inner and outer segment of the photoreceptor was more frequently affected, with associated focal damage of the outer nuclear layer. Defects of the retinal pigment epithelium were occasionally detected. These changes did not correspond to threshold burns on color fundus photography but corresponded to focal areas of increased autofluorescence in the majority of the cases.

SUMMARY

We concluded that raster scanning using high quality OCT does permit observation of the evolution of drusen and that 20% of drusen regress over a median time of two years. 51% appear stable and the remaining increase in size. The SD OCT seen progression of drusen causes a damage of the IS/OS-junction. After drusen regression the IS/OS-junction is either able to restore as drusen regress or was artifactitiously compressed, and not initially visible due to the initial drusen compression of the IS/OS junctional line. Therefore, caution is needed when analyzing the IS/OS junction integrity in eyes with subretinal deposits of any abnormal material. Disappearance of IS/OS junction does not

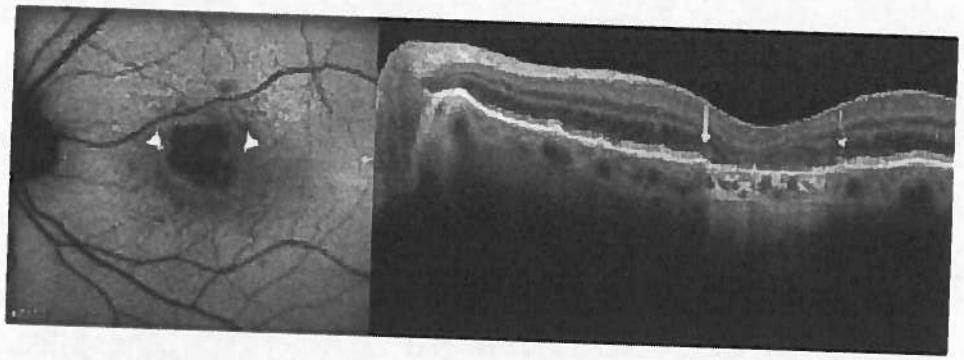
mean that photoreceptors are irretrievably lost, but size of subretinal drusen is correlated with reduction in microperimetric sensitivity as shown by our other studies. SD OCT can quantify abnormal and normal retinal and RPE tissue. Drusen volume, as determined by spectral domain-OCT, correlates with AREDS-determined drusen area and AREDS grade, in non-exudative AMD. The correlation is not perfect, however, because drusen area and volume average 40% and 82% of the variation, respectively. Drusen volume can provide additional information in grading the severity of eyes with dry AMD. Our group is working with several companies and engineers on new algorithms to automatically identify retinal layers. Disruption of the retinal photoreceptor layer as analyzed by spectral domain optical coherence tomography/scanning laser ophthalmoscope can be detected even in small areas. SD OCT clearly can detect subtle RPE changes in many types of retinal degenerations.

B. Fundus Autofluorescence

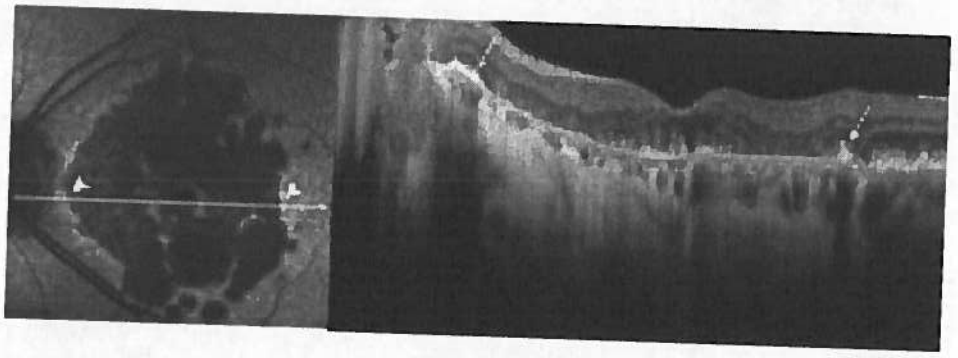
In geographic atrophy and in certain retinal degenerations, autofluorescence of the fundus (blue autofluoresence) has been suggested to predict progression and may be an important marker to evaluate in studies of therapy of GA. We hypothesized that the hyper autofluorescent banding is due to stressed and abnormal photoreceptors that are diseased but still surviving. We thus hypothesized that SD OCT might show this as a physical change not just a functional change seen by autofluorescence. Thus, we studied this association in the following paper: **Brar M, Kozak I, Cheng L, Bartsch DU, Yuson R, Nigam N, Oster SF, Mojana F, Freeman WR: Correlation between spectral-domain optical coherence tomography and fundus autofluorescence at the margins of geographic atrophy. Am J Ophthalmol. 2009;148(3):439-44.**

We performed a novel evaluation of AF and simultaneous SD OCT to see if there was a correlation between the two tests. We used spectral-domain OCT (Spectralis Heidelberg Retinal Angiograph/OCT; Heidelberg Engineering, Heidelberg, Germany; or OTI Inc, Toronto, Canada) as well as autofluorescence imaging (Heidelberg Retinal Angiograph or Spectralis; Heidelberg Engineering). The outer retinal layer alterations were analyzed in the junctional zone between normal retina and atrophic retina and were correlated with corresponding FAF. In a series of 23 eyes of 16 patients between 62 and 96 years of age,

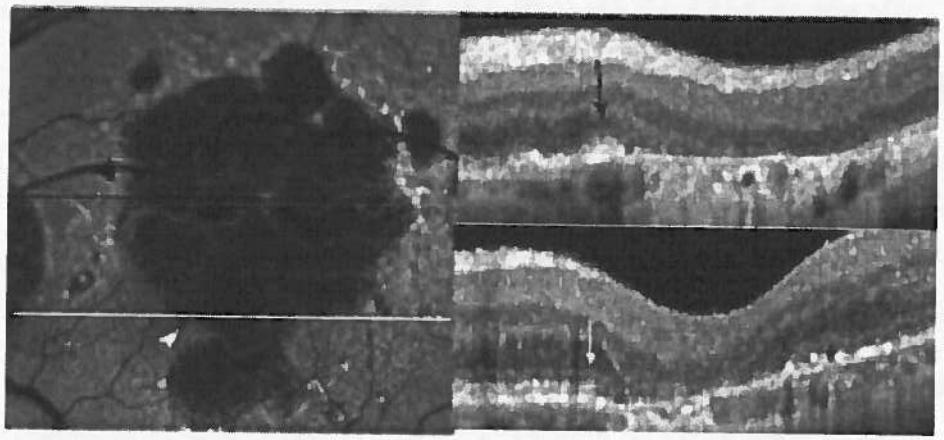
there was a significant association between OCT findings and the FAF findings ($r = 0.67$; $P < .0001$). Severe alterations of the outer retinal layers at margins on spectral-domain OCT correspond significantly to increased autofluorescence; smooth margins on OCT correspond significantly to normal FAF (kappa, 0.7348; $P < .0001$).



Above figure shows Fundus autofluorescence (FAF) and spectral-domain OCT images from a 74-year-old man with geograhic atrophy. (Left) FAF image showing no abnormal increased autofluorescence at the margin. (Right) Horizontal scan on OCTshowing atrophic outer retina with loss of normal reflectivity of the ELM, IS/OS junction, outer nuclear layer, and thin RPE with increased choroidal transmission. Outside the geographic atrophy area, retinal layer structures appear normal and margins are smooth and sharp with no abnormal activity at the level of the RPE. Arrowheads (left) and arrows (right) correspond to areas of no FAF at the margins.



Above shows FAF and spectral-domain OCT images from an 87-year-old woman with geographic atrophy. (Left) FAF image showing a continuous band of abnormal increased autofluorescence at the margins of geographic atrophy. (Right) Corresponding spectral-domain OCT image showing severe alterations in the outer retinal layers at the margins of geographic atrophy. Arrows indicate increased hyperreflectivity, irregularities, and thickening at the level of RPE with loss of ELM. Arrowheads indicate corresponding area on FAF image.



Above figure shows FAF and spectral-domain OCT images with horizontal scans at 2 different levels in a patient with geographic atrophy. (Top right) Spectral-domain OCT image showing irregular margins with structural alterations at the outer retina (black arrow) corresponding to increased FAF (black arrowhead) at the nasal margin. (Bottom right) Horizontal scans through the area of no abnormal FAF (white arrowhead) showing smooth margins on (Left) the spectral-domain OCT (white arrow).

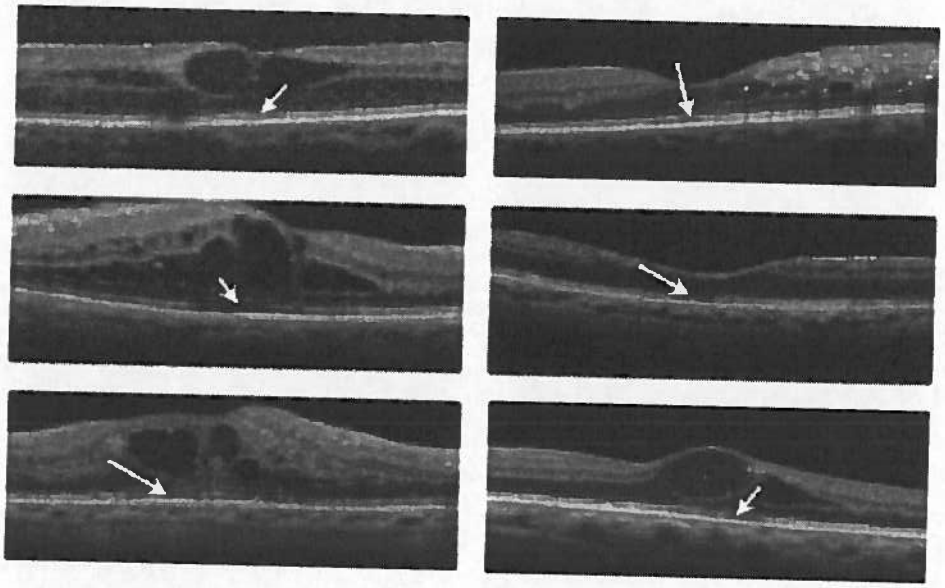
SUMMARY

We concluded that spectral-domain OCT provides in vivo insight into the pathogenesis of geographic atrophy and its progression. Visualization of reactive changes in the retinal pigment epithelial cells at the junctional zone and correlation with increased FAF; secondary to increased lipofuscin may serve as determinants of progression of geographic atrophy. Indeed, it is likely that SD OCT is as good a predictor of geographic atrophy progression as FAF and also can be used to determine lesion size.

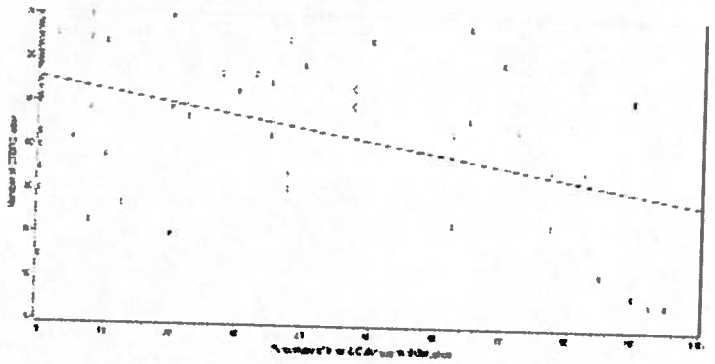
C. Imaging to Determine Photoreceptor Integrity

We determined if imaging of photoreceptor structure would predict vision or visual improvement. As photoreceptors become diseased, edematous or die, the loss of the IS OS junction or possibly the ELM (external limiting membrane) should be a marker for damage. For this reason, we evaluated the integrity of the photoreceptor inner segment/outer segment (IS/OS) junction using spectral-domain optical coherence tomography in patients with macular edema and to correlate the relationship between the integrity of the IS/OS junction and visual acuity: **Maheshwary AS, Oster SF, Yuson RM, Cheng L, Mojana F, Freeman WR: The association between percent disruption of the photoreceptor inner segment-outer segment junction and visual acuity in**

diabetic macular edema. Am J Ophthalmol. 2010;150(1):63-67. In this study, 62 eyes underwent SD OCT imaging. For each patient, two experienced observers masked to visual acuity measured several SD OCT variables, including central macular thickness, retinal volume, global disruption scale of outer retina, percentage disruption of the outer retina, and history of previous treatments. Visual acuity recorded as number of Early Treatment Diabetic Retinopathy Study letters was used as the outcome variable in univariate and multivariate analysis testing the measured SD OCT variables as predictors. In this study, we found a statistically significant correlation between percentage disruption of the IS/OS junction and visual acuity (P = 0.0312). Additionally, there was a strong trend suggesting a relationship between macular volume and visual acuity, although borderline significance was found (P = .07).



Above are six spectral-domain optical coherence tomography images through the fovea showing photoreceptor inner segment-outer segment (IS/OS) junction layer disruption on in patients with diabetic macular edema. The photoreceptor IS/OS layer was evaluated 500 μm in either direction of the fovea. The IS/OS disruption was graded from 0 to 2. Grade 0 was assigned when an intact IS/OS layer was found, grade 1 was assigned when focal disruption of the Is/OS of the IS/OS junction of 200 μm or fewer was found, and grade 2 was assigned when focal disruption of the IS/OS junction of more than 200 μm was found. The percentage of disruption along the IS/OS layer, again measured 500 μm in either direction of the foveal center, was recorded. The percentage disruption was averaged to generate a number between 0% (no IS/OS disruption) and 100% (total loss of the IS/OS layer in both horizontal and vertical scans). The arrowhead corresponds to the IS/OS junction: (Top right and Top left) intact IS/OS junction with grade 0 disruption; (Middle right and Middle left) disrupted IS/OS junction with grade 1 disruption, and (Bottom right and Bottom left) disruption IS/OS junction with grade 2 disruption.



Above scatterplot shows the relationship between visual acuity and increasing photoreceptor inner segment-outer segment (IS/OS) junction disruption on spectral-domain optical coherence tomography (SD OCT) in patients with diabetic macular edema. Patient vision acuity, expressed as the Early Treatment Diabetic Retinopathy Study (ETDRS) letters read, over the percentage of IS/OS junction disruption, was judged from the SD OCT images and is shown with a regression line. The graph demonstrates the decline of visual acuity with the increasing disturbance of the IS/OS layer of the photoreceptors. The regression coefficient was -0.30 after adjusting for volume effect, indicating that for each percent increase of IS/OS disruption, vision decreased by 0.3 ETDRS letters.

We also studied the IS/OS layer (associated with photoreceptor integrity) in eyes with inner retinal disease due to epiretinal membranes. **Oster SF, Mojana F, Brar M, Yuson RM, Cheng L, Freeman WR: Disruption of the photoreceptor inner segment/outer segment layer on spectral domain-optical coherence tomography is a predictor of poor visual acuity in patients with epiretinal membranes. Retina. 2010;30(5):713-718.** Traditionally, vision changes are thought to be associated with distortion of the retina and also from edema due to leakage from traction of the ERM on the retinal vessels. We hypothesized however that ERM's do eventually damage photoreceptors and wished to evaluate the predictive value of spectral domain-optical coherence tomography-determined integrity of the photoreceptor inner segment/outer segment (IS/OS) junction on visual acuity in patients with epiretinal membranes (ERMs). We studied 54 eyes from 48 patients with primary ERMs who underwent spectral domain-optical coherence tomography scans. Regression analysis was used to calculate the relative contribution of several variables, including photoreceptor IS/OS disruption, grade of IS/OS disruption, macular thickness, and ERM grade on fundus imaging to visual acuity. We found that the strongest individual predictor of visual acuity among patients with ERM was central retinal thickness on spectral domain-optical coherence tomography ($r^2 = 0.16$, $P = 0.0024$), but the most efficient model was the combination of

macular thickness and presence or absence of photoreceptor IS/OS disruption ($r^2 = 0.24$, $P = 0.0008$). Additional measured variables did not significantly contribute to visual acuity prediction. Inner segment/outer segment layer integrity was also an independent predictor of visual acuity, and patients with IS/OS disruption were 6.88 times as likely to have 20/50 or worse vision than patients with intact photoreceptor layers (odds ratio: 6.88, confidence interval: 1.56-30.43, $P = 0.01$).

SUMMARY

The disruption of the photoreceptor IS/OS junction is an important predictor of visual acuity among patients with macular disease. We conclude that disruption of the photoreceptor IS/OS junction is a statistically significant predictor of poor visual acuity among patients with ERM, dry AMD and other macular diseases and is most useful when combined with central retinal thickness measurement. Certainly evaluation of the photoreceptor IS/OS junction should be a part of imaging studies in retinal degenerations but better software is needed to do this in an automated way.

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#3- NEER DSMB 2011 Summary Memo

National Neurovision Research Institute
Accelerating Clinical Research to Cure Retinal Degenerations

11435 Cronhill Drive
Owings Mills, MD 21117
Ph: (410) 568-0150
Fax: (410) 363-2393
TDD: (410) 363-7139

October 12, 2011

MEMORANDUM
via E-mail

To: VPA Study Investigators

From: Steven Bramer, Ph.D.
Chief Drug Development Officer

Subject: Fall 2011 Report from the NNRI Data and Safety Monitoring Board (DSMB)

The NNRI DSMB met via conference call on September 28, 2011. At this meeting, the board reviewed accumulated safety and operational data from the VPA study. At that time, 13 study participants from 2 enrolling sites had been randomized with a maximum of 3 months of follow-up. Based on this data review, the DSMB had no safety concerns and recommended the continuation of the VPA Study.

The next formal data review by the NNRI DSMB is scheduled for the Spring 2012.

Copy: Stuart Fine, M.D., Chair, NNRI DSMB

#4- NEER DSMB 2012 Meeting Summary Memo

National Neurovision Research Institute
Accelerating Clinical Research to Cure Retinal Degenerations

Suite 100
7168 Columbia Gateway Drive
Columbia, MD 21046
Ph: (410) 423-0600
Fax: (410) 872-0574
TDD: (410) 872-0639

May 3, 2012

MEMORANDUM
via E-mail

To: VPA Study Investigators

From: Judith Chiostri 5/3/12
Director, Clinical Development, National Neurovision Research Institute (NNRI)

Subject: Spring 2012 Report from the NNRI DSMB

The NNRI DSMB met via conference call on April 30, 2012. At this meeting, the board reviewed accumulated safety and operational data from the protocol *A Phase II Multiple Site, Randomized, Placebo-Controlled Trial of Oral Valproic Acid for Retinitis Pigmentosa* (VPA Study). At that time, 19 study participants from 2 enrolling sites had been randomized with a maximum of 12 months of follow-up. Based on this data review, the DSMB had no safety concerns and recommended the continuation of the VPA Study.

The next formal data review by the NNRI DSMB is scheduled for the Fall 2012.

Copy: NEER Network CCC

#5- ProgStar Natural History Feasibility Rpt

The Natural History of the Progression of Geographic Atrophy Secondary to Stargardt's Disease

The ProgStar Study – Feasibility Survey

Drug Development Phase: N/A

Sponsor:

Foundation Fighting Blindness
7168 Columbia Gateway Drive
Suite 100
Columbia, MD 21046

Principal Investigator:

Hendrik P.N. Scholl, M.D., M.A.
The Dr. Frieda Derdeyn Bambas Professor of Ophthalmology
Retina Division of the Wilmer Eye Institute
The Johns Hopkins University Medical School
748 Maumenee Building
600 North Wolfe Street
Baltimore 21287-9277
Phone: (443) 287 5495
e-mail: hscholl1@jhmi.edu
Fax: (410) 614 2186

Introduction

Stargardt's macular dystrophy (STGD) is one of the most frequent causes of early macular degeneration and accounts for 7% of all retinal dystrophies . It is an autosomal recessive condition characterized by a bilateral loss of central vision occurring relatively early in life. Mutations in the gene (ABCA4) encoding the photoreceptor-specific, ATP-binding cassette transporter ABCR are responsible for STGD. Such defects may be responsible for the accumulation of lipofuscin and A2E which are toxic to the retinal pigment epithelium (RPE) in high concentrations, lead to cell death and atrophic lesions. The healthy RPE has fluorophores that can visualized by Fundus Autofluorescence and hence RPE lesions are detectible by Fundus Autofluoescence. Other retinal diseases like

age-related macular degeneration (AMD) share some similiarities like RPE-atrophy. Fundus Autofluorescence has recently been accepted as a primary outcome measure for the GATE-Trial that investigates the medical treatment effect on atrophic lesions due to AMD.

So far, there is no proven treatment option for STGD available. However, several therapeutic options are actually under evaluation. First, there is the approach of medical treatment. Evidence supports the notion that the formation of ocular lipofuscin is dependent on the aberrant reactivity of dietary vitamin A, in particular its ability to dimerize. Several compounds (retionids) are being developed to treat STGD and a clinical phase I trial will start in fall of this year/spring of 2013 at two sites in the United States. A second option is gene-therapy and as a third stem cell therapy is on the way. Both of the last mentioned are in clinical trials already under investigation.

However, for these upcoming possible treatment options, there is a strong need to define outcome measures and to learn about their variability to design clinical trials appropriately. Especially, the influence of such new therapies on the longitudinal outcome compared to the natural course of STGD will be crucial and therefore the natural course must be known. Such outcome measures should be accurate, reproducible and show only a small intra- and interobserver variability. Possible objective outcome measure can primarily be the progression rate of RPE atrophy in FAF; as a second outcome measure, changes in retinal morphology as determined by spectral-domain optical coherence tomography (sd-OCT) could be considered: recent advances in this imaging technique enable an non-invasive in vivo cross-sectional imaging of the retinal ultrastructure providing a resolution that could be only achieved so far by light-microscopy. Functional testing is possible by microperimetry (MP-1).

So far, little is known about the natural course of STGD in the sense of such objective measurements in a larger number of patients. Therefore a survey was conducted to get an idea of the possibility to collect data from different sites that are specialized in the treatment of patients with retinal dystrophies.

Methods

A questionnaire was sent to ten centers, seven in the United States and three located in Europe/United Kingdom.

Invited for responding were:

- Dr. Sunness (Greater Baltimore Medical Center, Baltimore, MD)
- Dr. Sahel (Centre de Recherche INSTITUT DE LA Vision, Paris, France)
- Drs. Webster & Moore (UCL Institute of Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust, London, United Kingdom)
- Dr. Zrenner (Pathophysiology of Vision, University Eye Hospital, Eberhard-Karls University, Tuebingen, Germany)
- Dr. Fishman (Chicago Lighthouse for People Who are Blind or Visually Impaired, Chicago, IL)
- Drs. Jacobson & Cidecyan (Center for Hereditary Retinal Degenerations, Scheie Eye Institute, Philadelphia, PA)
- Dr. Birch (Retina Foundation of the Southwest, Dallas, TX)
- Drs. Pierce & Berson (Boston)
- Dr. Weleber (Casey Eye Institute, Portland, Oregon)
- Dr. Bernstein (Moran Center, University of Utah School of Medicine, Salt Lake City, Utah)

The complete questionnaire is attached (please see attachment1 for details). Basically it requested the patient population (how many patients with STGD are in the database (seen within the last two years), how many have atrophic lesions, how many would be available for further follow-up). Further questions regarded data collection (how many patients have benn genotyped, which equipment was used to record data like microperimetry, fundus autofluorescence and optical coherence tomography. For the last, the specific type of machines had been to be specified.
The questionnaire was sent to the sites on April 9th, 2012.

Results

There was broad agreement to the need of a study that reflects the natural course of Stargardt's disease in respect to evaluate possible clinical outcome measures. All responses (100 %) were positive, i.e. in favor of the study. However, one site did not have the data on the primary endpoint(s), that is the measurement of atrophic lesions by Fundus autofluorescence and one site does not have the capacity to participate on such a study.

There are some examples of responses:

- Dr. Jacobson: "Very much needed and the right timing."
- Dr. Sahel: "All are willing to join efforts. Please tell me more specifically how we can promote together this important endeavour."
- Dr. Cideciyan: "We are in complete agreement that aspects of the natural history of ABCA4 disease need to be evaluated carefully in order to appropriately design upcoming clinical trials."
- Dr. Birch: "I totally support a multi-center attempt to make sense of Stargardt progression."

Table 1 summarizes the results: it shows that datasets of more than 400 patients available for retrospective data analysis and more than 200 patients would be available for a prospective natural history study.

Table 1: Summary of survey results

	Sunness (Baltimore)	Sahel (Paris)	Webster (London)	Zrenner (Tuebingen)	Fishman (Chicago)	Jacobsen (Philadelphia)	Birch (Dallas)	Bernstein (Soult Lake City)	Σ
# STGD patients	64	80	200	144	48	25	35	36	632
# STGD patients with atrophic lesions	55	15	185	100	40	20	30	33	478
# STGD patients with atrophic lesions available for F/U	55	15	60	30	N/A	20	30	20	230
# of pat. with ABCA4 mutations	26	60	160	50	31	20	30	36	413
Microperimetry	MP-1 (49), OPKO	MP-1 (3)	MP-1, MP-2	MP-1 (35)	MP-1 (11)	MP-1	MP-1	Maia	
Fundus Autofluorescence	HE	HE HRA classis, HE HRA-2	HE HRA classis, HE HRA-2, Fundus camera Optos	HE Spectralis, HE HRA classis, HE-HRA 2, Fundus camera	HE Spectralis	HE Spectralis, HE HRA classis, HE-HRA 2	HE Spectralis	HE Spectralis	
Sd-OCT	HE Spectralis, ZeissCirrus, OPKO	HE Spectralis	HE Spectralis	HE Spectralis	HE Spectralis, OPKO	Optovue	HE Spectralis	HE Spectralis	

Discussion

The results of the survey reveal that (relying on the site answers) over 400 patients would be available for the retrospective and assumably more than 200 patients could be enrolled in a propsective arm of a study that invetigates the natural course of Stargardt's macular dystrophy. There are several issues to consider: so far, STGD has been an untreatable entity. Counseling patients (including genetic counseling) and providing with low vision aids has been the only option. It is of special interest that in the field of inherited retinal dystrophies (including STGD) now three approaches are on the way: medical, gene-therapy and stem cell therapy. Each new treatment option has to been measured according to the natural course of the disease. In this context the statement for example by Dr. Jacobsen highlights that such a study is „very much needed and the right timing".

Due to the prevalence of STGD and limited number of patients in each (although specialized) center available, only a multicenter approach can tackle this topic. Given the sum of patients available at the eight centers listed above, a sufficient number of patients are available.

Regarding the fact that several treatment options are either already in or at least on the way to early phase clinical trials, it is also a matter of time to get results. Therefore a hybrid-design should be considered to be the best proposal including a retro- and a propsepctive arm. In the retrospective arm, a higher number of patients with the possibility of even a longer follow-up offers the option to get long-time follow-up data; the propsective arm will enable the center to follow up patients according to standardized procedures.

In conclusion, a multicenter study about the natural course of STGD is justified.

Attachment 1: Questionnaire

The Natural History of the Progression of Atrophy Secondary to Stargardt's Disease Survey

Protocol No.: NNRI-STARG-01

Patient Population

1. How many patients with the clinical diagnosis of Stargardt's disease are in your database that have been seen in your clinic at least twice in the past two years? _____
2. How many of the patients from question #1 have atrophic lesions (by fundus autofluorescence as defined in the protocol synopsis)? _____
3. How many of the patients listed above would be available for follow-up evaluations in the next 12 months? _____

Data collection

4. Please provide a rough estimate of how many of the patients as specified in question #1 above were screened for ABCA4 mutations: _____

5. Which of the following equipment have you used to record data from the patient number as specified in question #2 (check the box)?
   a. MP1 Yes ☐ No ☐
      i. If yes, how many patients have you collected MP1 data on? _____
      ii. What MP1 protocol was used (e.g. 10-2 protocol)? _____

   b. Fundus Autofluorescence (FAF) Imaging Yes ☐ No ☐
      i. If yes, how many patients have you collected FAF data on? _____
      ii. If you used Near-Infrared FAF Imaging, how many patients have you collected NIA data on? _____
      iii. What machine are you using for the FAF imaging?
         ☐ Heidelberg Engineering HRA classic/HRA2
         ☐ Heidelberg Engineering Spectralis
         ☐ Fundus Camera, 30 degree photo
         ☐ OPTOS wide-field Autofluorescence
         ☐ Other (please specify)

   c. OCT Imaging Yes ☐ No ☐
      i. If yes, how many patients have you collected OCT images of the macula? _____
      ii. What machine/Protocol are you using for the OCT?
         ☐ Heidelberg Engineering Spectralis
         ☐ ZEISS, Stratus
         ☐ ZEISS, Cirrus
         ☐ Optovue
         ☐ Other (please specify) _____

#6- ProgStar Design Meeting Minutes

Protocol about the PROGSTAR Design Meeting, August 8th, 2012 – Columbia, MD

Participants:

Protocol Principial Investigator:	Hendrik PN Scholl
Sponsor - FFBCRI Team:	Patricia Zilliox, Judy Chiostri
Site Principial Investigators:	Hendrik PN Scholl, Gerald Fishman, Janet Sunness, David Birch, Samuel Jacobson, Paul Bernstein, Jose Sahel (Teleconference), Eberhart Zrenner, Michel Michaelides
Stargardt Expert Advisors/FFB Advisory Board Members:	Richard Weleber, Johanna Seddon
National Eye Institute:	Frederick Ferris, Brian Brooks, Wadih Zein, Brett Jeffrey
Johns Hopkins Coordination, Data, and Statistics Team:	*Research Team* of Dr. Scholl: Emily Fletcher, Rupert Strauss, Yulia Wolfson, Stacey Seabrook *Wilmer Biostatistics Center*: Ann Ervin, Beatriz Munoz
Reading Center (Doheny Image Reading Center, Keck School of Medicine, USC):	Vas Sadda
Data Monitoring (EMMES):	Donna Brown

Purpose of the meeting

The objective of the meeting was to develop a study design and to define outcome measures to be validated in the Natural History of the Progression of Atrophy Secondary to Stargardt's Disease (PROGSTAR) Study for the use in future treatment clinical trials.

1. Welcome and Introduction of Participants

Welcome address by Patricia Zilliox, Bill Schmidt, Hendrik Scholl.

2. Background and Rationale of the ProgSTAR study

Dr. Scholl presented on the rationale of the study.
In summary, he pointed out:

- A multi-center natural history study on the progression of STGD1 is needed.
- Main outcome measure will be lesion size as defined by FAF imaging.
- Secondary outcome measures are photoreceptor layer integrity as measured by sd-OCT, retinal sensitivity as measured by microperimetry and visual acuity.
- The study will help to define outcome measures for clinical trials.
- The study will also help to establish technology, trial sites and reading centers.
- The study will characterize the progression of STGD1 and may provide crucial information to design clinical trials for STGD1.

Subsequently Patricia Zilliox summed up that the FFB had already previous meetings in 2006, 2008 and 2010 before meeting the FDA; summaries were provided in written form in a folder to the participants. Particularly, it was pointed out that in these meetings with the FDA that visual acuity (VA) alone is not sufficient as a primary outcome measure from the FDA perspective. Several companies are deveolping compounds to treat STGD and it was discussed in which ways different companies maybe fund/assist trials in the future. Dr. Ferris commented on this with his experience in trials regarding diabetic retinopathy.
Then he addressed the issue of „fuzzy border" brought forward by the FDA. Every measurements (even in VA) has its fuzzy borders (maybe called mean and standard deviation), but it is unclear what the FDA means by „fuzzy borders". It was stated that attention should be paid to the transition zones as clinical trials with compounds that will improve the condition will be different from that dealing with compounds that will slow down progression (looking for delta between treated and untreated group).
Dr. Ferris expressed his concerns about geographic atrophy as an outcome measure,. Some progression may be related to nonperfusion in the region of GA like in AMD that may grow irrespective to treatment. Progression may go on despite treatment at least for a while, and time may be an issue, for example as some RPE-cells can be in such a bad

shape that GA progression might go on for one year and therefore the sample size could be too small. Additionally other underlying pathophysiologies for progression of geographic atrophy should be taken into account. Furthermore the issue whether the observation of „fleck-like" lesions could be possible was discussed (like drusen in AMD). At the end it was stated that function is crucial for FDA, and proof of principle is important.

3. Presentation of the Feasibility Survey and Proposal of the Reading Center

Dr. Scholl presented the results of the feasibility survey that lead to the proposed ProgSTAR design. Subsequently the proposed reading center was introduced to the participants. It was argued that different possible reading centers were screened and that the group of Dr. SriniVas Sadda may provide optimal resources for the study both providing the requested strategies and set-up (e.g. algorithms to compare data from different machines and centers) as well as from a scientific point of view.

4. Natural history

Dr. Gerald Fishman gave an illustrative overview over the natural history in Stargardt's disease to stimulate the discussion. Especially he pointed out the need to preserve central visual acuity and that good outcome measures are needed.

5. Therapeutic approaches to Stargardt's

In the following presentation Dr. Paul Bernstein presented the current therapeutic approaches to STGD beyond light and vitamin A restriction like visual cycle inhibition (RPE 65 inhibitors...), inhibitors of A2E-formation and restorative approaches (restoration of ABCA4 function, RPE rejuvenation, removal of lipofuscin).

6. Value of Fundus Autofluorescence as a primary outcome measure

In the next presentation Dr. Scholl brought forward the arguments to use Fundus Autofluorescence (FAF) as a primary outcome measure for the ProgSTAR study and Emily Fletcher demonstrated the region finder in Heidelberg Spectralis OCT as a tool to track lesion growth in STGD. In the following discussion several points were addressed like there might be different thresholds for different patients (here, the proposed reading center could provide help in drawing manually), inter-grader variability and the value of this approach. Especially discussion arose about the value in comparison with

OCT which may be more accurate and reproducible and the proven loss of tissue could be easier accepted by the FDA. For analysis of the data (area in FAF), the suggestion was made to use the square root transformation to normalize the distribution, because the radius could be a better outcome measure rather than square area.
In conclusion, it was assessed that both FAF and OCT will be evaluated in the study and for FAF, a standard operating procedure with fixed setting of sensitivity was suggested. Dr. Scholl confirmed the rationale to choose the change in lesion size assessed by FAF as this approach is accepted and approved in the GATE-trial. However, as the planned study is also explorative in nature, he emphasized how important it is to stay open-minded and to evaluate the possibilities of the OCT which provides several types of measurements like the outer nuclear layer etc.

7. Sd-OCT in STGD; strategies for segmentation analysis

To address the last point in a better way, David Birch illustrated in his following talk the segmentation possibilities like manual segmentation or evaluation of transition zones. Adressing some points of previous discussions he showed that the mentioned „fuzziness" may come from the fact that different layers show abnormalities at different locations. For example, the outer nuclear layer (ONL+) begins to decrease before anything else in STGD, therefore this layer could be an outcome measure as well. Volumes can also be calculated using multiple scans, therefore manual segmentation comes to a point.
Regarding the limits in automated segmentation algorithm Dr. Scholl reminded that in STGD it could be easier performed than in AMD. It was broadly agreed that OCT shows cellular levels which makes it easier for dealing with the FDA in the future and is more sensitive than function (psychophysical tests) whereas FAF reflects pathophysiology STGD and may also reflect future treatment effects given the compounds in development.
Regarding Fundus Autofluorescence, the issue of patient's exposition to light was addressed. These original concerns arose from animal models in studies by Dr. Jacobson's group. These concerns about light toxicity will be addressed in a way to consider a reduction of the excitation (should be easier done in patients of younger age with clear optical media like Stargardt's patients). These should be achieved by optimizing SOPs and thereby it can be tried to obtain quantitative FAF (or at least) semi-quantitative (a recent publication by Peter Charbel-Issa was mentioned). One crucial

point will be a fixed sensitivity setting on the Spectralis/HRA2 when obtaining these images.

8. Total Macular Volume as a potential outcome measure in sd-OCT

In a short presentation Dr. Strauss introduced the variable „total macular volume" that is provided by the Spectralis software algorithm as a potential outcome variable with some of its advantages and disadvantages.

9. Microperimetry in STGD

Dr. Sunness presented on the value of microperimetry (MP) in STGD and its implications. She showed that dense scotoma may significantly exceed the visible atrophic lesion in STGD and visual acuity can improve as part of the natural history. She also demonstrated the bimodal peak reading rates in eyes with macular ring scotoma. Furthermore she proposed three different potential test strategies for MP in the trial. In the following discussion it became obvious that a compromise has to be made to setup a test strategy that is feasible for all centers and the need to standardize it. Especially two proposals will be further discussed. One contains a stimulus along the foveal line (as published by Dr. Jacobson's group). In this case, Dr. Birch pointed out that it would be of importance to define the foveal scan by Spectralis OCT and import that into the MP-1. Furthermore it was propsed to use the 10-2 strategy but reduced it by about 50 % of stimulus points.

There was a consensus that function as an outcome measure should be regarded in view to structure-function correlations. If MP-1 data support those findings from sd-OCT, a stronger position for upcoming clinical trials can be achieved. Again it was emphasized that at least some standardization is needed (including possible training effects in patients which lead to reproducible results).

10. Rod-driven responses as functional outcomes (ERG b-wave recovery after photobleach)

Dr. Zrenner introduced the objective assessment of b-wave recovery after bleach in STGD patients for phenotype differentiation up to discussion in the way of degree of rod involvement and degree of visual cycle slow down in relation to FAF and central geographic atrophy. Especially he rose the question whether b-wave recovery after bleach could be a good predictor of functional and morphological outcome in natural

disease history, as this function´s dynamics may be closely related to ABCA4 mechanisms of all-*trans* retinal clearing.

As seen in the following consensus, the majority of participants voted for the inclusion of an ERG at least at baseline examination on one eye in the prospective arm of the study.

11. Phenotype-Genotype- Phenotype-Correlation in STGD

In the last presentation Dr. Michealides provided some interesting insights about their experiences with genotype-phenotyoe correlations at the Moorfields Hospital, London including some aspects in consanguine patients.

In the following discussion several issues were addressed. Dr. Scholl encouraged to look at two hypotheses:

1.) look at homogenous mutations in both alleles.

2.) categorize mutations types non null mutations versus null.

He argued that genotyping is essential: the additional data can be of advantage for cohorts in upcoming clinical trials. In Dr. Jacobsen's point of view it should be the obligation to find and identify patients at our best. Dr. Brooks suggested a modified genotyping with two definite mutations and wouldn't exclude the earliest most severe onset.

Consensus

In the following the alterations of the originally proposed study protocol synopsis are provided:

1. Genetics

A. if not a typical phenotype of STGD exists, two mutations in ABCA4 are required.

B. In case of „classic" phenotype presentation, the proof of one mutation is sufficient

C. Patiens with RDS mutations are to be excluded

There is the possibility to include several patients from one family (consanguinity)

2. Full-Field ERG

There is no requirement for the retrospective arm of the study, however for the prospective arm, at least one full-field-ERG on least one eye is required at baseline examination.

3. Age

After an intensive discussion about the inclusion criteria regarding age of patients, consensus was found to set the age at 12 years or older. For the case that, at the discretion of the investigator, the pediatric patient will be able to perform all the required tests reliably, then younger patients can be considered for enrollment.

4. Retrospective arm

The inclusion criteria additionally to the presence of a atrophic lesion as defined before and genetic testing as stated above:

- The primary study eye must have clear ocular media and adequate pupillary dilation to permit good quality of imaging modalities used
- Patients have been followed for at least 2 visits and were followed for at least 2 years, and had at least one examination in addition to visual acuity (out of: Fundus Autofluorescence; SD-OCT, Fundus Photography, Fluorescein Angiography, Microperimetry)

5. Reading Center

In recognition of the fact that not only standard procedures but also flexibility and scientific interest are required and the options for that profile of qualification are limited, it was accepted to entrust Dr. Sadda and his coworkers at Doheny with the task of the reading center.

7. Other inclusion and exclusion criteria

- Ocular disease in either eye that may confound assessment of the retina both morphologically and functionally. Therefore, choroidal neovascularization, glaucoma and diabetic retinopathy must be excluded.
- Ocular surgery in the primary study eye within 90 days prior to Baseline visit
- The primary study eye must have at least one well-demarcated area of atrophy as imaged by fundus autofluorescence with a minimum diameter of 300 microns, and all lesions together less than or equal to 12 mm^2 (≤ 5DA –Disc area) and BCVA 35 ETDRS letters (20/400 Snellen equivalent) or better.

Furthermore it was stated that being symptomatic is **not** an inclusion criteria.